THE EFFECTIVENESS AND COST-EFFECTIVENESS OF IMATINIB FOR FIRST LINE TREATMENT OF CHRONIC MYELOID LEUKAEMIA IN CHRONIC PHASE

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CONFLICTS OF INTEREST

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Background
Chronic Myeloid Leukaemia (CML) is a rare blood cancer with an incidence of 1.0 per 100,000 for men and 0.8 per 100,000 for women. In CML, an excessive number of leukaemic white blood cells are produced that suppress the production of normal white blood cells. In 95% of cases a specific chromosomal abnormality, the Philadelphia chromosome, is present. This is a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9. The consequent molecular abnormality is a fusion protein, BCR-ABL, which is a tyrosine kinase. There are three identifiable phases of chronic myeloid leukaemia: chronic, accelerated and blast phase with blast phase being fatal within 3 to 6 months.

CML is not currently curable with conventional chemotherapy or immunotherapy. Patients diagnosed in the chronic phase may expect a median of 3-5 years survival. Bone marrow transplant (BMT) offers a cure but is only available to a minority of people.

Current drug treatments include interferon-alpha (IFN-α) and hydroxyurea (HU). Imatinib is a new treatment that works by blocking the ATP binding site on the BCR-ABL tyrosine kinase. Imatinib has already been recommended for treatment of patients in all phases of the disease who have failed treatment with IFN-α.

Objective
This assessment evaluates the effectiveness of imatinib as first line treatment for those with chronic myeloid leukaemia in chronic phase compared to IFN-α, HU and BMT and the cost-effectiveness of imatinib compared to IFN-α and HU.

Methods
A systematic review of the literature was undertaken. Searches of electronic databases, websites and reference lists were made to identify relevant studies. All studies of imatinib were included, along with RCTs of IFN-α compared to hydroxyurea and comparative studies of BMT compared to IFN-α. Studies were only included if they were of adults in chronic phase and were published in English.

The titles and abstracts of studies and full text articles were screened independently by two reviewers for inclusion. Using a structured form, the quality (internal and external validity) of the included studies was assessed by one reviewer and checked by a second reviewer.

Due to the lack of homogeneous randomised controlled trials (RCTs) we have not performed meta-analysis. We have, however, provided comparative data where available. The assessment includes all patient relevant outcome measures reported by the studies.

Survival is the key outcome measure. Surrogate outcome measures include haematological (blood) response (HR) and cytogenetic (bone marrow) response (CR). Based on the current evidence and knowledge of the effect of imatinib, it is generally considered that the relationship between cytogenetic response and survival is sufficiently strong to support the use of CR as a surrogate outcome measure.

Results
One RCT comparing imatinib with IFN-α+Ara-C was identified. Four RCTs comparing IFN-α to HU were included along with five studies comparing BMT and IFN-α. The study comparing IFN-α+Ara-C to imatinib was of reasonable quality with the main potential biases being the lack of blinding (patient, physician, outcome measurement and data analysis), the potential for bias in the assessment of quality of life, and the high crossover and attrition

rates. The study reports on relatively short-term outcomes (12 months for the majority of this analysis). The studies comparing IFN-α and HU were of reasonable quality with lack of blinding and allocation concealment being the main potential biases. The BMT trials were of variable quality with lack of randomisation, blinding, power calculation and groups that differed at baseline.

Intention-to-treat analysis showed that imatinib was associated with complete CR at 12 months follow-up of 68% compared to 20% for the IFN-α+Ara-C group ($p<0.001$). The estimated proportion of people taking imatinib who had not progressed to accelerated or blast phases at 12 months was 98.5% and 93.1% for IFN-α+Ara-C ($p<0.001$). Overall survival was not statistically significantly different between the two groups with death rates of 2% and 3.8% for imatinib and IFN-α respectively. Withdrawal due to side-effects was 2% for imatinib compared to 5.6% for IFN-α and cross over due to intolerance was 0.7% for imatinib compared to 22.8% for IFN-α+Ara-C. Quality of life was better in the imatinib group compared to the IFN-α group when assessed at 1, 3 and 6 months using the FACT-BRM instrument.

Median survival across the four IFN-α versus HU studies was 66 months (range 61-76 months) for IFN-α compared to 56.2 months (range 52-66 months) for HU. Median complete CR was 6% (range 4-9%) for IFN-α compared to 0 (range 0-1%) for HU. Median withdrawal due to side-effects was 24% (range 18-25%) for IFN-α compared to 4% (range 1-4%) for HU.

Four out of the five studies comparing BMT and IFN-α showed a long-term survival advantage for BMT compared to IFN-α, but a short-term (0-4 years approximately) disadvantage. In four of the five studies comparing BMT and IFN-α median survival had not yet been reached in the BMT groups in 6-10 years. Median survival in the IFN-α arms ranged from 5.2-7 years. The BMT group gained a survival advantage over IFN-α at between 3-5.5 years. In the BMT group death due to transplant related complications ranged from 36% to 45% (median 38%).

Cost-effectiveness

A search of the economic literature revealed no published cost-effectiveness studies comparing imatinib and IFN-α. An independent Markov model was constructed and this was compared to models submitted to the National Institute for Clinical Excellence (NICE) by the manufacturer of imatinib, Novartis. The incremental cost-effectiveness ratio (ICER) of imatinib compared to IFN-α from the independent model was £26,180 per QALY gained (ranging from £13,555 to £51,870) and was relatively robust when subjected to a number of sensitivity analyses. This figure is similar to industry estimates of between £18,000 and £26,000. Imatinib was less cost-effective when compared to HU with an ICER of £86,934. Probabilistic analysis showed that if the decision-maker was willing to pay £27,000 per QALY, then imatinib had a greater probability of being cost-effective than IFN-α. With three comparators, HU, IFN-α and imatinib, HU is most likely to be cost-effective until willingness to pay is greater than £86,000. However, this treatment may be appropriate first line only in occasional circumstances, such as frail or very elderly people. The ICER between HU and imatinib is high, predominantly due to large cost differences between the treatments.

Conclusions

Imatinib appears to be more effective than current standard drug treatments in terms of cytogenetic response and progression free survival with fewer side-effects. However there is uncertainty concerning longer-term outcomes, the development of resistance to imatinib, the duration of response, and the place of imatinib relative to BMT. New issues are continually arising such as the optimal management pathways, and combination therapies. Longer-term follow-up data and future research will assist in answering these questions.

LIST OF ABBREVIATIONS

2-CdA	2-chlorodeoxyadenosine
17-AAG	17-allylamino-17-demethoxygeoldanamycin
ABL	Abelson oncogene
Ara-C	Cytosine arabinoside
ATP	Adenosine triphosphate
BCR	Breakpoint Cluster Region
BM	Bone marrow
BMT	Bone marrow transplant
BNF	British National Formulary
BU	Busulphan
CML	Chronic Myeloid Leukaemia
CR	Cytogenetic response
CRD	Centre for Reviews and Dissemination
CRKL	CRK oncogene like protein
CY	Cyclophosphamide
DNA	Deoxyribonucleic acid
ECOG	Eastern Co-operative Oncology Group
EMEA	The European Agency for the Evaluation of Medicinal Products
EQ-5D	European Quality of Life Instrument
F-ara-A	Fludarabine
FACT-BRM	Functional Assessment of Cancer Therapy- Biological Response Modifier
FCE	Finished consultant episode
FDA	Food and Drug Administration (U.S.A)
FISH	Fluorescence in situ hybridisation
GRC	Global Rating of Change scale
GVHD	Graft versus host disease
HLA	Human Leukocyte Antigen
HU	Hydroxyurea
HR	Haematological response
ICER	Incremental cost-effectiveness ratio
IFN-α	Interferon-alpha
IM	Imatinib
Int	Intermediate
IRIS	International Randomised Study of Interferon + Ara-C vs. STI571 in CML
ITT	Intention-to-treat
LDAC	Low dose cytosine arabinoside
MU	Mega-units
MUD	Matched unrelated donor
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PBSC	Peripheral blood stem cells
PCR	Partial cytogenetic response
PEG	Pegylated
PFS	Progression free survival
Ph+	Philadelphia positive cell
PHR	Partial haematological response
PISCES	PEGIntron and imatinib/STI571 combination evaluation study
QALY	Quality adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Relative risk
RT-PCR	Reverse transcriptase polymerase chain reaction
SCT	Stem cell transplantation
SE	Standard error
SPIRIT	STI571 prospective international randomized trial
STI-571	Imatinib
WBC	White blood cells

DEFINITION OF TERMS

Abelson oncogene	An oncogene is a cancer-causing gene. The Abelson oncogene is located on that part of chromosome 9 that translocates to chromosome 22 in chronic myeloid leukaemia.
Allogeneic transplant	A bone marrow or stem cell transplant using marrow from another person. If the marrow is from an identical twin, it is termed syngeneic.
Allopurinol	A drug used to control excessive white blood cells and to minimise the build up of blood uric acid.
Autologous transplant	A bone marrow or stem cell transplantation using the patient's own marrow which is removed, treated and stored before administration.
Basophilia	An excess number of basophils, a rare type of white cell, found in the peripheral blood.
Blast cells	Immature cells found in and produced by the bone marrow. Not normally found in the peripheral blood.
Bone Marrow	The soft substance that fills bone cavities. It is composed of mature and immature blood cells and fat. Red and white blood cells and platelets are formed in the bone marrow.
Breakpoint Cluster Region	The region of on a chromosome where breaks cluster. In the case of CML, the narrow part of chromosome 22 where the translocation to chromosome 9 occurs which includes the Abelson oncogene (BCR-ABL). The BCR-ABL protein product results in the excessive proliferation of a tyrosine kinase.
Bone marrow transplant	A procedure where a patient's bone marrow is replaced by healthy bone marrow. The bone marrow to be replaced may be deliberately destroyed by high doses of chemotherapy and/or radiation therapy. The replacement marrow may come from another person, or it may be previously harvested from the patient's own marrow.
Chemotherapy	The treatment of a disease by chemicals to destroy cancer cells. Chemotherapy can affect the whole body.
Cyclophosphamide	Preconditioning treatment for bone marrow transplantation
Cytogenetic response	A response to treatment at a level of chromosomal abnormalities. In the case of CML, assessed by counting the number of Ph+ cells in metaphase (usually 20 metaphases are analysed). A complete response reveals no Ph+ cells, a partial response leaves up to 35% Ph+ cells evident and with a minor response from 35% to 95% Ph+ cells are still evident.
Cytopenia	A reduction in the number of cells circulating in the blood.
CRKL	An adapter protein that becomes tyrosine phosphorylated by BCR-ABL.
EQ-5D	A European quality of life questionnaire containing five physical and psychological dimensions.
Erythrocytes	Red blood cells which carry oxygen around the body and carbon dioxide back to the lungs.
Extramedullary disease	Disease occurring outside the bone marrow.
Fibroblasts	Connective tissue cells.
Gompertz function	A function used to estimate survival curves.
Graft versus host disease	A complication of bone marrow transplantation where there is a reaction of donated bone marrow against a patient's own tissue. It can be fatal and is due to the donor's immune cells recognising the host cells as foreign.
Haematological response	A haematological response refers to the normalisation of blood cell counts. CML causes over proliferation of WBCs and treatments aim to lower these. Typically, the response is classified as complete (WBC <10 x 10^9/l, platelets <450 10^9/l, no immature cells in the peripheral blood with normal differential count, and disappearance of symptoms and signs.
Hydroxyurea	A drug used in the treatment of CML which inhibits DNA synthesis.
Incremental cost effectiveness ratio	Demonstrates the total additional cost per QALY gained of one alternative over another. There is no particular point at which an alternative is said to be "cost effective" as this will be a policy decision. The larger the incremental cost effectiveness ratio the less likely it is to be cost effective.
Interferon-α	Interferon is a protein derived from human cells. It has a role in fighting viral infections by preventing virus multiplication in cells. IFN-α (alpha) is made by leucocytes. It is often used as first line therapy in CML.
Landmark analysis	A form of survival analysis where only patients who have survived a specified period of time are included in the analysis.
Leukocytes	White blood cells which are responsible for fighting infections.
Leukopheresis	A process of removing excess white blood cells from the peripheral blood.

Leukopenia	A reduced number of white cells in the blood – it may affect a single cell type or all white cells.
Matched unrelated donor	Unrelated allogeneic transplant (MUD) --The person donating marrow is unrelated to the patient. The chances of finding an unrelated compatible donor from the general population depends on the rarity of the individual's tissue type. Genetic and ethnic background can also affect the likelihood of finding a donor.
Metaphase	The second phase of mitosis (cell division). Cells in this phase of division are used for cytogenetic analysis in CML to identify the proportion of Ph+ chromosomes.
Mitosis	A division of cells which consists of four phases - prophase, metaphase, anaphase and telophase.
Myelocytes	Committed progenitor cells produced by, and found in, the bone marrow which develop into mature leukocytes.
Neutropenia	A decrease in neutrophils (white blood cells) circulating on the blood.
Neurotoxicity	Poisonous to the nervous system.
Peripheral blood	In this report, peripheral blood refers to blood in the circulatory system
Promyelocytes	Committed progenitor cells produced by and found in the bone marrow which develop into myelocytes.
Radiation therapy	Treatment using high-energy radiation from X- or other rays intended to damage cancer cells and stop them multiplying.
Stem cells	Very early progenitor cells which divide and mature to become all the types of cells which make up the blood and immune system.
Thrombocytes	Platelets (fragments of bone marrow cells) found in the blood which help to form clots and control bleeding.
Thrombopenia	A reduced number of thrombocytes (platelets) in the blood.
Toxicity	The quality of being poisonous. The National Cancer Institute (NCI) grade toxicity levels of treatments as 1 – mild, 2 – moderate, 3 –severe and 4 – life-threatening.
Tyrosine Kinase	An enzymatic protein which adds phosphate residues to other proteins in the cell. In CML the abnormal tyrosine kinase, BCR-ABL, phosphorylates proteins which cause cellular proliferation.
Weibull curve	A mathematical function which is often used in modelling to describe survival times, and in which the chance of survival varies with time.

1 AIM OF THE REVIEW

To assess the effectiveness of imatinib as first line treatment for those with chronic myeloid leukaemia in chronic phase compared to IFN-α, HU and BMT and the cost-effectiveness of imatinib compared to IFN-α and HU.

2 BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

2.1.1 Natural history and clinical presentation of Chronic Myeloid Leukaemia

Leukaemia is a rare type of cancer affecting the blood. Chronic Myeloid Leukaemia (CML) is the third most common type of leukaemia. In CML the bone marrow produces an excessive number of abnormal stem cells (the precursor cells of white cells, red cells and platelets). The abnormal cells eventually suppress the production of normal white blood cells that act to protect the body against infection.

Three phases of CML are usually identifiable; the chronic phase, an accelerated phase and the blast phase. The accelerated phase is seen in about two-thirds of patients; others progress directly to the blast phase. Transition between the phases may be gradual or rapid. Typically, the annual progression from chronic to blast phase is 5-10% in the first two years and 20% in subsequent years.[1]

Chronic Phase

The chronic phase is the initial, usually relatively stable and benign phase of CML and generally lasts 3-5 years from diagnosis. During this period malignant progenitor cells proliferate rapidly but retain their ability to differentiate. Progression of CML is due to the gradual loss of differentiation potential of malignant cells.

In the chronic phase there are less than 10% blasts and promyelocytes (immature cells) in the bone marrow. There is an elevated white cell count, including basophilia, and often an elevated platelet count in the peripheral blood. Because the disease progresses slowly, it is difficult to detect in its early stages. In 40% of sufferers, CML is only discovered when a routine blood test or examination for an unrelated disorder is performed.[1]

The majority of patients are in chronic phase at presentation. The main clinical findings are:

- Fatigue or looking pale due to anaemia. This is often the symptom that leads people with CML to seek medical advice.
- A feeling of `fullness' or a tender lump on the left side of their abdomen due to enlargement of the spleen (Half of all patients have splenomegaly). Sometimes the liver is also enlarged.
- Fever and/or night sweats.
- Weight loss may also be apparent.

Accelerated phase

The accelerated phase marks the transition to the blast phase, typically lasting up to 18 months[2] but sometimes leading to a rapidly fatal blast crisis within 6 months. No single set of criteria for its onset is accepted. However, in some cases accelerated phase is defined as between 5% and 30% blasts in the peripheral blood and bone marrow. Other authors use greater than 15% blasts as a definition.[3] Symptoms in accelerated phase may include feeling fatigue (due to anaemia), infections, bruising or bleeding.

Blast phase

The blast phase is usually fatal within 3-6 months of onset. The presence of 30% or more blast cells in the marrow or any blast cells within the peripheral blood defines the blast phase. Clinically, it is characterised by signs and symptoms such as fever, sweats, pain, weight loss, and enlarged lymph nodes, liver or spleen.

2.1.2 Epidemiology

All types of leukaemia account for 2.1% of all cancers in England and Wales[4] and the sex ratio for men:women is 1.7:1. In 1997, 531 new cases of CML were diagnosed in England; an annual rate of 1.0 per 100,000 for men and 0.8 per 100,000 for women.

While CML is rare below the age of 20, it does occur in all age groups. People registered in trials of interferon treatment for CML have median ages between 47-56 years at study commencement.[5-7] A trial of imatinib reports median age at commencement of 51 years[8] and trials of BMT report lower median ages of 31-36 years.[9-12]

Academic publications tend to report younger populations than population registries. This may reflect selection practices in clinical trials and bias arising from studies being carried out in tertiary care institutions.

National cancer registers may not be notified of all cases but are likely to be more representative of all people with CML than those enrolled in clinical trials. A local registry of patients in North East England gives a median age at onset of between 60 and 69 years.[13] A population based survey of CML patients in Norway found a median age at onset of 62 years.[14]

Prevalence is difficult to estimate given varying estimates of survival. Based on 3-5 year median survival times, there are probably about 3000-3500 people with CML in England and Wales, or approximately 90-105 people per Strategic Health Authority area of 1.5 million people.

2.1.3 Aetiology, pathology and prognosis

Molecular mechanisms

In 95% of cases of CML, patients have a genetic abnormality caused by a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9

(the Philadelphia chromosome) [15]. This is not an inherited abnormality but is acquired by individual stem cells. As a result, proliferation of both mature and immature white blood cells occurs in the bone marrow and the blood.

The Abelson oncogene (ABL) is located on chromosome 9. In CML this translocates to the BCR gene on chromosome 22. As a consequence, an abnormal protein, a tyrosine kinase, is formed. Patients with CML who do not have the Philadelphia chromosome have complex or different translocations which still result in the formation of the BCR-ABL gene and its product.

Tyrosine kinases function as part of the internal communication network of the cell regulating processes such as proliferation, differentiation and survival.[16] In chronic myeloid leukaemia, the BCR-ABL protein product results in the production of a tyrosine kinase which is not controlled by normal cellular mechanisms. The cells containing the abnormal gene and protein replicate quickly, and may be protected from programmed cell death (apoptosis). They therefore come to predominate, initially in the bone marrow and subsequently in the bloodstream. By the time these cells are detected in the bloodstream, the disease process is well underway. Patients with CML at presentation or relapse usually have a total burden of more than 10^{12} malignant cells.[17] Several additional complex genetic abnormalities are acquired during progression of CML and are implicated in progression of disease. However, molecular mechanisms underlying the development of CML and the inevitable transformation to blast crisis are not completely understood.[18] For example, the BCR-ABL abnormality can be detected in people who have not developed CML.[19]

Survival

A study in 1924 by Minot reported an average survival in untreated patients of 36.6 months.[20] Seventy-five years later, a population-based survey in Norway also described a median survival of 36 months, with an estimated 5 year survival rate of 33%.[14] Survival is also dependent on other medical conditions, which are prevalent in the elderly population, such as heart and respiratory disease. A significant proportion (30%) of people with chronic phase CML die from an unrelated condition.[14]

However, in the literature, IFN-α trials report a median survival of 63-76 months.[5;7;21] This is likely to refer to a younger and more selected population than is seen in routine clinical practice.

Changes in the availability of blood testing and, possibly, earlier presentation and diagnosis over time, suggest that length of survival is not comparable between cohorts established at different times. This may be due to lead-time bias[22] and developments in adjunctive treatment, such as more effective anti-infective agents.

Risk scores

Several risk-scoring systems have been developed which categorise people with chronic phase CML into risk groups that reflect their survival prognosis. The most common is the Sokal score, although other prognostic scores have also been developed (see Appendix 10.1, page 87). In clinical practice, knowledge of individual risk scores may inform treatment decisions. The three Sokal categories represent those with good prognosis (low risk), those with intermediate prognosis (intermediate risk) and those with poor prognosis (high risk). Expected median survival for CML

patients treated with chemotherapy at high, intermediate and low risk has been estimated at 2.5, 3.5 and 5 years respectively.[23]

The Sokal score has been shown to perform less well as a prognostic indicator among people receiving IFN-α treatment compared to those treated with HU or BU chemotherapy. In response to this, a newer prognostic score (the Hasford or IFN-α score) was developed (see Appendix 10.1, page 87).[24]

Both Sokal and Hasford scores have been shown to be predictors of survival.[5;25-27] The Benelux CML Study Group report that the Sokal score is discriminatory for survival in patients receiving HU, but not for patients receiving IFN-α.[5] Hehlmann and colleagues report that stratification according to risk group has a greater effect on survival than treatment allocation in patients receiving IFN-α, HU or BU.[26] This suggests that risk profile is an important potential confounder in comparisons of treatment and should be taken into account, preferably through the use of randomisation in the context of direct comparisons.

Both risk score systems have shown a significant association with haematological and cytogenetic response (with low risk patients responding quicker and keeping their response longer; for definitions of haematological and cytogenetic response see section 2.3.2, page 24).[25] Risk category and haematological response in particular are strongly associated (p=0.002 for the Hasford score and p=0.005 for Sokal). For both, the association is less strong for cytogenetic response, and the new score has a weaker association than the Sokal score (p=0.061 for the Hasford score and p=0.01 for Sokal).[28]

It has not been possible to validate the Hasford measure in people treated with imatinib due to the lack of longer-term survival data, but clinical consensus is that the Hasford score will also be applicable to this treatment group.

2.1.4 Significance in terms of ill-health

Little published evidence is available about the quality of life in people with CML or those who are taking various treatments for CML. People diagnosed with CML may not have any symptoms. Others may present with fatigue, a tender abdomen, a temperature, night sweats or weight loss. As the disease progresses symptoms worsen and it may be difficult to differentiate the symptoms of disease from the side-effects of treatment.

The side-effects of IFN-α and chemotherapy have been well documented. A substantial minority of people cease treatment with IFN-α due to intolerance or have their doses adjusted.[29] Clinical consensus is that the adverse effects of IFN-α have a major impact on quality of life. The psychological benefits of taking a drug in a trial situation with the possibility of long-term gain may, however, be sufficient to outweigh the effect of the symptoms on quality of life.[30].

Quality of life is not solely determined by the adverse effects of therapy – the physical consequences of the disease itself and the psychological effects of knowing the poor prognosis with CML may be important determinants.[31] It has also been suggested that a strong determinant of quality of life in chronic leukaemia is reaction to the uncertainty of living with this disease.[31] In these circumstances, the adverse effects

of treatment may play a relatively small part for some patients although individuals' experiences will differ. Taking all these factors into account CML is likely to have a significant and increasing impact on quality of life throughout its course.

2.2 CURRENT SERVICE PROVISION

2.2.1 Current service provision

CML is not currently curable with conventional chemotherapy or immunotherapy. Most treatments aim to return the patient to the chronic phase of the disease. Treatment depends on the overall health and age of the patient and, for bone marrow transplantation, the availability of a suitable matched bone marrow donor. Clinicians suggest that older, frailer patients are offered much more limited treatment alternatives and may, in practice, be restricted to HU. More detailed information on treatment options is shown in Section 2.3 (page 23).

There were 7,366 finished consultant episodes (FCEs) for CML (4,322 male) in 1999-2000. FCEs count each episode of care delivered under a single consultant during each period of hospital stay (as a day-case or in-patient). This means that each patient may be counted a number of times. The median age of consultation was 51 from this data source. Age distribution is shown in Table 1. This difference from cancer registries may be due to more intensive hospital based therapy, such as BMT, among younger CML patients which accounts for greater numbers of FCEs among this age group. These FCEs represent 7,133 hospital admissions, 5,317 of which were day cases. A total of 18,206 bed days were accounted for by CML. Much of CML therapy is given as an outpatient, and hence will not be recorded in these statistics.

Table 1 Number of FCEs for CML in England 1999-2000

Age	Number
0-14	189 (3%)
15-59	4,541 (62%)
60-74	1,798 (24%)
75+	838 (11%)
Total	7,366

2.2.2 Current options for treatment

This section gives a brief overview of the main current treatments for CML, other than imatinib, which is discussed in section 2.3.1 (page 23).

Interferons

Interferons are a complex group of naturally occurring proteins with potent multiple effects on immunity and cell function. IFN-α therapy was introduced in the 1980s and regulates cytokine expression and inhibits haematological growth factors. It is also an immunomodulator (alters T cell reactivity), and is directly cytotoxic for some tumour cells.[29;32] However, the exact basis for the effects of IFN-α in CML is not known, and may vary from person to person.[25] Throughout this report interferon refers to IFN-α.

Daily injections are needed and relatively high doses have to be given to induce a cytogenetic response. Most people experience adverse effects, at least initially. These factors reduce treatment adherence. Interferon alpha has a toxic profile producing both acute and chronic adverse effects. Because of this, clinician consensus is that many older or frailer patients are not suitable for treatment with IFN-α. Such patients may make up a significant proportion of the CML population.

The effect of combining IFN-α with other agents such as cytarabine (Ara-C) has been shown to improve cytogenetic response and survival compared with IFN-α alone but increases toxicity.[18;33-35] However, this combination is not currently licensed in the UK. [36] There are reports that IFN-α is now being used in combination with imatinib.[37]

More recently, pegylated IFN-α has been used for CML. The addition of a polyethyleneglycol molecule to IFN produces a molecule with a longer half-life and more favourable pharmacokinetics. These characteristics permit a once per week injection. Pegylated IFN-α has been used in combination with imatinib and is thought that it may have a synergistic effect. High rates of grade 3 and 4 haematopoietic toxicity (77%) have been reported with pegylated IFN-α although non-haematological events appear minimal and results are still in very early stages.[38;39]

Hydroxyurea

Until the advent of IFN-α therapy, HU was considered the standard treatment for newly diagnosed patients. Hydroxyurea suppresses the excessive multiplication of the myeloid peripheral cells by inhibiting one of the enzymes involved in DNA replication. Hydroxyurea relieves symptoms with few adverse effects and produces haematological remission in over 90% of patients. However, it has little or no effect on cytogenetic response. It is generally accepted that HU can modestly prolong survival compared to busulphan, which is associated with more adverse effects.[22]. Hydroxyurea is often used in combination with IFN-α, when IFN-α fails, when IFN-α is not tolerated or in very elderly or frail people.

Bone marrow (BMT) or stem cell transplantation (SCT)

Allogenic bone marrow transplant is an appropriate comparative treatment for imatinib in only a small number of patients (less than one fifth of those eligible for drug treatments). It is currently the favoured treatment for young patients with CML in the chronic phase who have an available donor. Bone marrow transplant is associated with a high early mortality rate (20 to 40%) and therefore is only suitable for health people in relatively early stages of disease. It is not possible to receive a transplant unless a suitable donor is available as it is likely the transplant will be rejected. In this report BMT is briefly compared to imatinib through indirect comparisons of effectiveness. Bone marrow transplant is not, however, modelled in cost-effectiveness analysis due to the differences in eligible populations.

BMT and SCT have traditionally been the only potentially curative treatments for CML. Fifty to 55% of patients under 40 receiving BMT may remain disease free at 10 years.[40] Autologous BMT involves aspirating the person's own marrow when they are in remission, treating the marrow with myeloablative therapy and then reinfusing intravenously. Allogenic BMT involves donated marrow from a HLA identical sibling or a matched unrelated donor. The process involves aspirating marrow from the donor and infusing into the recipient. Autologous transplants are thought to be associated with the lowest mortality. Effectiveness is thought to be greatest for HLA-

identical sibling transplants, although advancing experience with techniques has led to reports that matched unrelated donor transplants can have equivalent outcomes.[41] Newer BMT techniques and preconditioning regimens are continually emerging.

There is a substantial transplant related mortality of between 20% and 40% with the main causes of death being infection, cytomegalovirus pneumonitis and graft-versus-host disease.[42] Currently less than one fifth of patients are both suitable for a BMT (are in good general condition and aged under 55) and have access to a donor.[1] The most favourable timing of the transplant is controversial, but is generally thought to be more successful if offered relatively early in the disease process.[1;43]

With the introduction of imatinib, more options have become available for people in whom BMT is possible. There may be a role for imatinib as part of a preconditioning regime, following BMT, or as a direct alternative. There is currently no published evidence to guide management in this area.

Other possible treatments not included in this assessment report

Peripheral Blood Stem Cells (PBSC) transplantation

This is a newer technique which involves obtaining and infusing peripheral blood stem cells rather than marrow cells. The procedure can be autologous or allogeneic. The advantage is thought to be faster haematopoietic cell reproduction than with marrow due to the cells from peripheral blood being more differentiated. The treatment may also be safer due to the shorter duration of neutropenia.[44] A published randomised trial reports that PBSC transplantations using HLA-identical sibling donors are superior to bone marrow transplantations with faster haematopoietic and immune recovery and the potential to reduce disease recurrence.[45].

Busulphan

Busulphan can control the signs and symptoms of CML through controlling blood count but has little or no effect on the progression of the disease. Busulphan is not regularly usually used for CML as it has less favourable survival and more side-effects than HU. For these reasons it is not considered further in this assessment.

2.2.3 Patient diagnosis

CML is diagnosed by the presence of a characteristic blood and bone marrow cellular pattern, together with cytogenetic and molecular diagnostic techniques.

Cytogenetic techniques detect the Philadelphia chromosome, and were originally considered the gold standard. Cytogenetic analysis requires the examination of at least 20-30 bone marrow cells in mitosis, so that the metaphases can be examined. There are considerable sampling errors because of the relatively small numbers of cells examined and the infrequency of measurement (bone marrow examination is invasive, which precludes frequent testing). The limit of detection is between 1% and 5% (i.e. it cannot detect less than 1% abnormal cells). The definition of minimal residual disease may vary in the literature.

Fluorescence in situ hybridisation (FISH) tests for the presence of the BCR-ABL gene, and may be positive in the absence of the Philadelphia chromosome. It uses a

fluorescent-labelled DNA probe to determine the presence or absence of a particular segment of DNA. In the case of CML it looks for the BCR-ABL fusion gene in bone marrow, or peripheral blood cells. In the FISH test, approximately 200 cells are examined making it more sensitive than the traditional cytogenetic count of 20-30 metaphases. It is susceptible to false positive results, and the limit of detection is considered to be between 1% and 5% abnormal cells.[46] The advantage of this technique is that cells do not need to be cultured or analysed in metaphase.[47]

Southern and Western blotting techniques have a similar sensitivity to FISH, but can be performed on peripheral blood.

Reverse transcriptase polymerase chain reaction (RT-PCR) is a very sensitive assay which tests for the presence of messenger RNA, the intra-cellular product that enables proteins to be produced from the DNA gene. Each messenger RNA is specific for the particular protein that it encodes. RT-PCR can detect a single leukaemia cell in 10^5 –10^6 normal cells.[48]

CRKL phosphorylation assay is a functional test that has been developed to detect intracellular activity of the BCR-ABL tyrosine kinase. This CRKL phosphorylation assay, is raised in people with CML, drops back to normal levels when the patient has a cytogenetic response, and then becomes elevated again with relapse. The sensitivity and specificity of this test is not yet clear.[49]

2.3 DESCRIPTION OF NEW INTERVENTION

2.3.1 Intervention- Imatinib

Imatinib mesylate (STI-571, also Gleevec® or Glivec®, Novartis Pharmaceuticals) is a rationally designed competitive inhibitor of the BCR-ABL protein tyrosine kinase. It is taken as a once daily oral dose.

Imatinib acts by blocking the ATP binding site on the BCR-ABL tyrosine kinase. This inhibition prevents the phosphorylation of the tyrosine residue on the attached substrate, reducing cellular proliferation. BCR-ABL has a long half-life and requires the continuous presence of inhibitors to substantially reduce its function.[18]

The recommended dose is 400mg/day for those in chronic phase CML escalating to 600mg/day in those whose disease progresses, do not haematologically respond within 3 months and those who lose a previously attained haematological response. The dose is administered orally and given once daily with a meal and a large glass of water.

Imatinib has previously been evaluated for NICE as second line treatment of CML in chronic phase and as first line treatment in accelerated and blast phases and the following guidance issued in September 2002:

> "Imatinib is recommended as a treatment option for the management of Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in chronic phase in adults who are intolerant of interferon-alpha (IFN-α) therapy or in whom IFN-α is deemed to have failed to control the disease." (NICE guidance appraisal no.50)

The guidance defines IFN-α failure as either a) failing to achieve a complete haematological response after 3 months of IFN-α treatment as monotherapy or in combination with HU or b) failing to achieve major cytogenetic response after 1 year of IFN-α treatment despite haematological response. IFN-α intolerance is defined as the presence of documented Grade 3 non-haematological toxicity, persisting for more than 2 weeks, in patients receiving a regimen that contains IFN-α. (NICE guidance appraisal no.50)

Furthe, the guidance states that

> "Imatinib is recommended as an option for the treatment of adults with Philadelphia-chromosome-positive CML in accelerated phase or blast crisis provided they have not received Imatinib treatment at an earlier stage." (NICE guidance appraisal no.50)

Imatinib is a designated orphan drug in the European Union and was first authorised in November 2001. The current EMEA product information states that:

> Glivec (i.e. imatinib) is indicated for the treatment of adult patients with Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (CML) in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

In December 2002 the USA Food and Drug Administration (FDA) and the EMEA issued a licence for imatinib in first line treatment of CML.

There is little published evidence for imatinib in the following populations: paediatric, prior to or following BMT, impaired hepatic function, moderate to severe impairment of renal function or overt cardiac disease.

2.3.2 Outcome measures

Cytogenetic and haematological response as intermediate outcomes

The achievement of a haematological and/or cytogenetic response has been suggested as an intermediate outcome in CML (i.e. as a proxy for long-term survival). It has been postulated that these responses indicate a reduction in the tumour burden, and therefore a reduction in the number of clonal, genetically unstable cells. This may, in turn, reduce the rate of secondary genetic change and postpone progression of the disease to blast crisis.[50] However, the effects of IFN-α in increasing cytogenetic abnormalities while prolonging survival suggest this may not be a straightforward relationship.[32] An alternative theory is that the cells destined to produce blast crisis are already present at the time of diagnosis, and time to progression depends on host factors and the doubling time of the blast cells.[51] The former theory, but not the latter, suggests that achievement of haematological and/or cytogenetic response is causally associated with prolonged survival.

Classification of cytogenetic responses is by bone marrow (BM) metaphase analysis as shown in Table 2.

Table 2 Classification of cytogenetic responses by bone marrow (BM) metaphase analysis

Degree of cytogenetic response	Percentage of BM metaphases remaining Ph+	
	Talpaz *et al.*, 1987 criteria	**Cortes *et al.*, 1996 criteria**
None	>95	>99
Minimal	35-95	35-99
Partial	5-34	1-34
Complete	0	0

NB: Combined partial and complete categories= Major

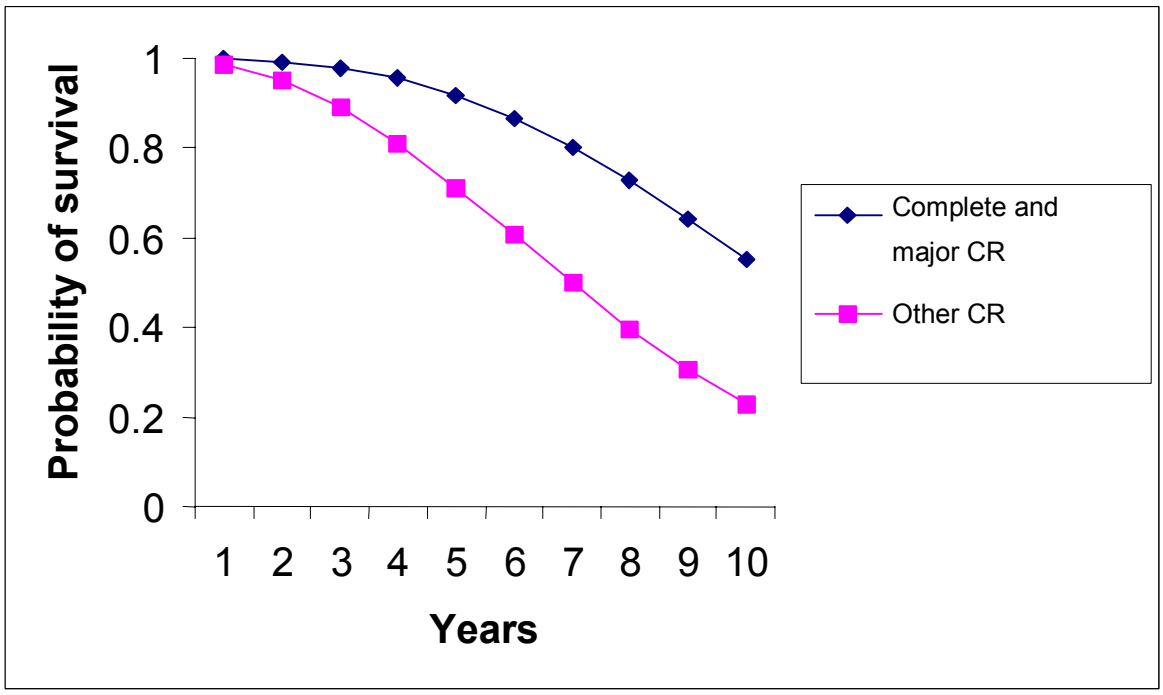
Haematological response to treatment refers to the normalisation of blood counts. Complete haematological response is defined as follows:

- WBC ≤ $10x10^9$/l, platelet ≤ $450x10^9$/l
- No immature cells in peripheral blood
- Absence of all signs of disease including splenomegaly
- Resolution of symptoms

In most trials, haematological response is reported as the best response achieved over the length of the trial follow-up.

Evidence relating to IFN-α does suggest that a complete HR or CR is indicative of longer survival. For example, the Italian Cooperative Study Group on CML reports that people with a complete CR had approximately 94% survival at 5 years compared to just under 70% in all others (Figure 1)[21]

Figure 1. Overall survival of interferon alpha patients who experienced a complete or major CR compared to any other CR. Figure derived from data presented in the Italian Co-operative Study [21]



In the previous NICE appraisal of imatinib for failed IFN-α therapy it was considered likely that "…based on the current evidence and knowledge of the effect of imatinib, that the relationship between cytogenetic response and haematological response and survival is sufficiently strong to support the use of cytogenetic response and haematological response as surrogate measures of efficacy." (Technology Appraisal Guidance – No. 50)

There is, however, still reason to be cautious. Responses to therapy may simply represent the identification of subsets of patients with better prognosis. If one therapy delivers prolonged survival compared to the alternative and is associated with higher rates of HR and CR, it is tempting to assume that HR and CR are on the causal pathway by which therapy influences outcome. However, it remains possible that HR and/or CR are an epiphenomenon, seen more commonly with a particular therapy, but which may not be produced by an alternative effective therapy. The appearance of CR and/or HR may not be associated with prolonged survival with an alternative therapy such as imatinib.

Therefore, the presence of a relationship between CR and HR and survival is not guaranteed to hold for imatinib. In the absence of long term follow-up data the assessment of such a relationship is not possible.

Even given the general clinical consensus that the relationship between cytogenetic response and survival is causal, there are still uncertainties regarding the duration of

response to imatinib and resistance. These issues may impact on the overall survival that is seen with imatinib in the longer term.

2.3.3 Duration of response and resistance

The duration of response to imatinib remains a crucial unanswered question. Recent follow-up data from a Phase 2 study suggests that survival with imatinib remains above 90% at 2 years

Imatinib's mechanism of action suggests that continual exposure to the drug is required. It is not known whether imatinib can ever be safely stopped. In contrast to this, longstanding un-maintained remission has been documented in a small number of people treated with IFN-α and some IFN-α treated patients remain in remission for 10 years.[29] It has been suggested that IFN-α can produce an 'operational cure' even though pathology is still detectable.[46]

Resistance to chemotherapy is a common feature of many cancers, and has been documented with imatinib. Disease progression is at least partly associated with the failure to maintain effective inhibition of BCR-ABL kinase activity[52] as measured by the CRKL assay. Secondary oncogenic changes that permit malignant proliferation independent of BCR-ABL are also possible, but appear to be less likely as an explanation.[53] It is probable that resistance will be an important determinant of long-term survival with imatinib and mechanism of resistance is discussed further in Appendix 10.2. (page 88).

Many aspects of imatinib therapy are still not understood. It is also unclear why some patients fail to achieve a response. Possibilities are:

- There is poorer inhibition of BCR-ABL by imatinib in less mature cells (i.e. a high proportion of immature cells are less sensitive to imatinib)
- Relatively resistant stem cells have a proliferation advantage and eventually predominate.
- The percentage of BCR-ABL positive stem cells may vary considerably between people.[36]

The ideal method of preventing resistance is to treat disease for as short a time as is needed to eradicate it. Practically, this may be difficult in CML.[54] Alternatively, studies have indicated that to obtain optimum efficacy and prevent drug resistance, combination therapy with other anti-neoplastic agents may be necessary.[54] Recently, studies have reported combining Imatinib with other agents such as 2-chlorodeoxyadenosine (2-CdA), fludarabine (F-ara-A),[55] IFN-α [37], pegylated recombinant interferon alfa2b,[38;39] Ara-C[56], 17-allylamino-17-demethoxygeldanamycin (17-AAG),[57] carboplatinum or etoposide, [54] gamma-irradiation and alkylating agents (such as BU or treosulfan).[58]

2.3.4 Anticipated costs

Imatinib costs £12.98 per 100mg. The approximate annual cost per patient for 400mg/day in the chronic phase is £18,951, and for 600mg /day in accelerated or blast phase is £28,426. Doses of 800mg/day will cost £37,902 per year per patient.

3 METHODS

3.1 Method for reviewing effectiveness

3.1.1 Search strategy

Three separate searches of electronic databases were performed to identify published studies and ongoing research (Appendix 10.3, page 90).

1. Imatinib

The search performed for the previous NICE assessment report on Imatinib as second line treatment for CML was updated. The previous strategy identified studies assessing first line treatment of CML. The search was not restricted by study design.

2. Interferon alpha versus hydroxyurea

We updated the previous NICE assessment report search for the comparison of HU and IFN-α. This search was restricted to randomised comparisons, as high-level evidence is known to exist.

3. Interferon alpha versus bone marrow transplant

We conducted searches to identify evidence for BMT versus IFN-α. No restrictions by date of publication were applied to this search.

All searches were restricted to English language and the search terms and strategy are outlined in Appendix 10.3 (page 90). Bibliographies of identified publications were searched for further relevant articles, handsearching of conference abstracts (European Haematology Association, American Society of Clinical Oncology, International Society for Experimental Hematology and American Society for Hematology) for Imatinib was performed and the manufacturers of Imatinib were approached for unpublished studies.

3.1.2 Inclusion and exclusion criteria

Two independent researchers (KD and AR) reviewed titles and abstracts for inclusion. The full text of articles deemed relevant were obtained and the two researchers independently reviewed each for final inclusion. Disagreements were resolved by consensus.

The following inclusion criteria were applied:

Study design:

Imatinib compared to any other treatment: studies with a control group only
IFN-α compared to HU: randomised controlled trials only
IFN-α compared to BMT: studies directly comparing IFN-α and BMT in the same study only

Stricter study design criteria were applied to comparison of IFN-α and HU due to the large number of randomised trials known to be available.

If studies were reported only in abstract form we tried to obtain the full text article. If a full text article was not available the abstract was excluded.

Population: Adults presenting for first line treatment of CML in chronic phase were included. Studies of patients in accelerated or blast phases were excluded.

Intervention and comparisons: Studies comparing the following were included:

Imatinib compared to any other treatment
IFN-α compared to HU
IFN-α compared to BMT

Studies of HU were only included if at least 75% of the control group received HU (e.g. at least 75% received HU and up to 25% received other agents such as BU). Relevant meta-analyses were only included if they reported all relevant outcomes that were present in the original reports of the RCTs, otherwise the original RCTs were included.

Outcomes: Quality of life, overall survival, haematological response, cytogenetic response and adverse effects were included.

3.1.3 Data extraction strategy

Data were extracted by one reviewer (KD) and checked by a second reviewer (RG). Response rates and survival were calculated where possible from original data presented in the reports and not from percentages given in the report, which are often adjusted for a variable number of dropouts. In some cases, survival was estimated from survival curves presented in the results.

3.1.4 Quality assessment strategy

Using a structured form, the internal and external validity of the included studies were assessed by one researcher (KD) and checked by a second (RG). The quality assessment of comparative studies was based on the following criteria:

RCTs/ comparative studies (CRD Report No. 4)

- Was the assignment to treatment groups an adequate method of randomisation?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were the outcome assessors blinded to the treatment allocation?
- Was the care provided blinded?
- Was the patient blinded?
- Were point estimates and measure of variability presented for the primary outcome measure?
- Was the analysis intention-to-treat?

The external validity was reviewed through consideration of patient characteristics including eligibility and inclusion/exclusion criteria.

3.1.5 Data synthesis

Due to the lack of suitable randomised evidence meta-analyses have not been performed. Data are described through narrative and summarised in tables.

No direct evidence comparing Imatinib with HU or BMT was identified. We have therefore calculated outcome measures directly from the relevant single arms of available trials to enable an approximate assessment of the efficacy of Imatinib in relation to these treatments. It cannot be emphasised too strongly that this kind of comparison is potentially biased, particularly in terms of potential differences in the populations studied, the variable completeness of follow-up, publication bias.

A further difficulty arises from the short-term follow-up in the Imatinib trial and the consequent reliance on HR and CR as proxy outcome measures for longer-term survival.

When 95% confidence intervals were not described in the original reports, these have been calculated wherever possible using STATA™.

3.2 Methods for economic analysis

3.2.1 Systematic review of existing economic literature

Electronic databases were searched for published economic studies. The economic search performed for the previous NICE assessment report on Imatinib as second line treatment for CML was updated. All economic studies of any treatment for chronic phase CML in adults have been included. Economic studies identified have been very briefly described and appraised using the Drummond checklist.[83]

3.2.2 Cost effectiveness and cost utility

A Markov model was developed to determine the incremental cost-effectiveness ratio of Imatinib compared to HU and IFN-α, and of HU compared to IFN-α in terms of cost per QALY. The model was constructed in Microsoft Excel. The model follows a cohort of 1000 people with CML from the time they commence treatment until death or for a total of 20 years (whichever comes first). The period 20 years was selected as a realistic period in which the majority of CML patient's lives could be hypothetically captured. The cycle length for the model is 3 months and costs are calculated based on an NHS perspective.

Basic assumptions

For a person diagnosed with chronic phase CML there are a number of possible treatment pathways. In this economic model, cohorts of 1000 CML patients progress through three alternative treatment pathways. We assume that all persons in this model are not candidates for BMT, and further, that people will change or stop treatment due to disease progression, or loss of response.

Figure 1 shows the possible transitions between health states for patients receiving first line treatment with hydroxyurea in the model. It is not possible to have a cytogenetic response when being treated with HU. It is possible to move to every other state from chronic phase, but once accelerated or blast stage has been reached, no return to chronic phase is possible.

Figure 1 Pathway for those with chronic phase CML treated with hydroxyurea

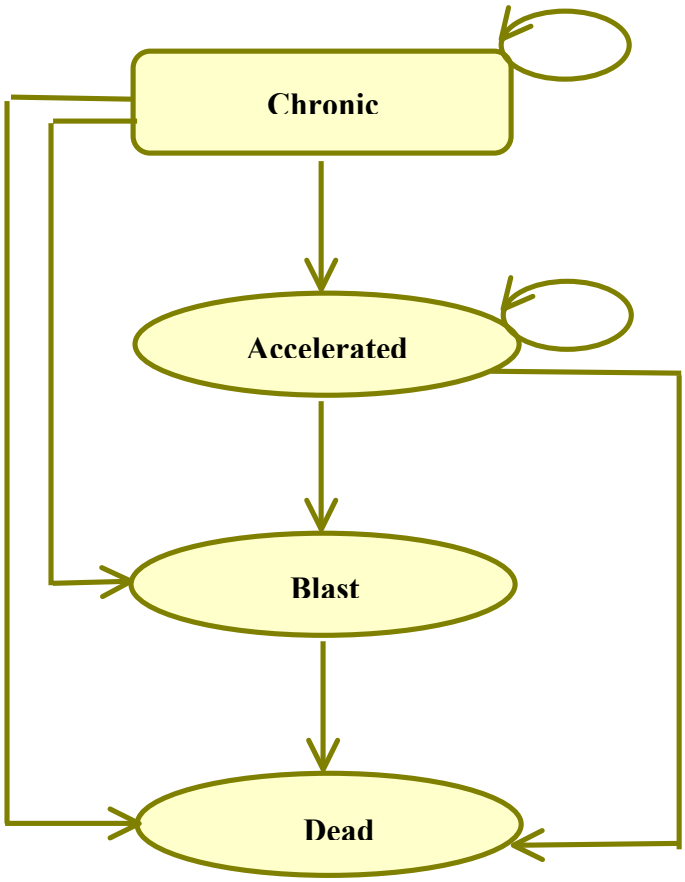


Table 3 shows the three treatment pathways that are compared in the model. The pathways each consist of first line treatment, treatment when disease progresses to accelerated phase, treatment when disease progresses to blast phase and treatment for those who lose their cytogenetic response.

Table 3 Treatment pathways for imatinib, interferon alpha and hydroxyurea

Treatment pathway	Starting treatment	Treatment when disease progresses to accelerated phase	Treatment when disease progresses to blast phase	Treatment for those who lose their cytogenetic response
1	Imatinib (400mg/day)	Interferon alpha	Mercaptopurine	Interferon alpha
2	Interferon alpha	Imatinib (600mg/day)	Imatinib (600mg/day)	Imatinib (400mg/day)
3	Hydroxyurea	Hydroxyurea	Mercaptopurine	Not applicable

Once patients are treated following disease progression or loss of CR, assumptions are also made regarding the probabilities of moving from one state to another (transition probabilities). When direct data are not available relative benefit or disbenefit (RR) of alternative treatments estimated from the literature are applied to available IFN-α data. Table 4 summaries the derivation of the transition probabilities used. They are calculated from rates reported in studies using the drug in question.

Table 4 Derivation of transition probabilities used in independent economic model

Treatment pathway	Starting transitions	Transitions when disease progresses to accelerated phase	Transitions when disease progresses to blast phase	Transitions for those who lose their cytogenetic response
1 **Imatinib (400mg /day)**	-Imatinib progression rates -Imatinib death rates -Imatinib response rates	-IFN-α progression rates -IFN-α death rates	Fixed death rate	-IFN-α progression rates -IFN-α death rates
2 **Interferon alpha**	-IFN-α progression rates -IFN-α death rates -IFN-α response rates	-IFN-α progression rates -IFN-α death rates X imatinib RR of survival	Fixed death rate X imatinib RR of survival	-Imatinib following failed IFN-α progression rates -IFN-α death rates X imatinib RR of survival
3 **Hydroxy-urea**	-HU progression rates -HU death rates	-HU progression rates -HU death rates	-Fixed death rate	Not applicable

For patients in pathway 1, treatment starts with imatinib and switches to IFN-α treatment on progression or loss of response. Subsequent cytogenetic response is not permissible.

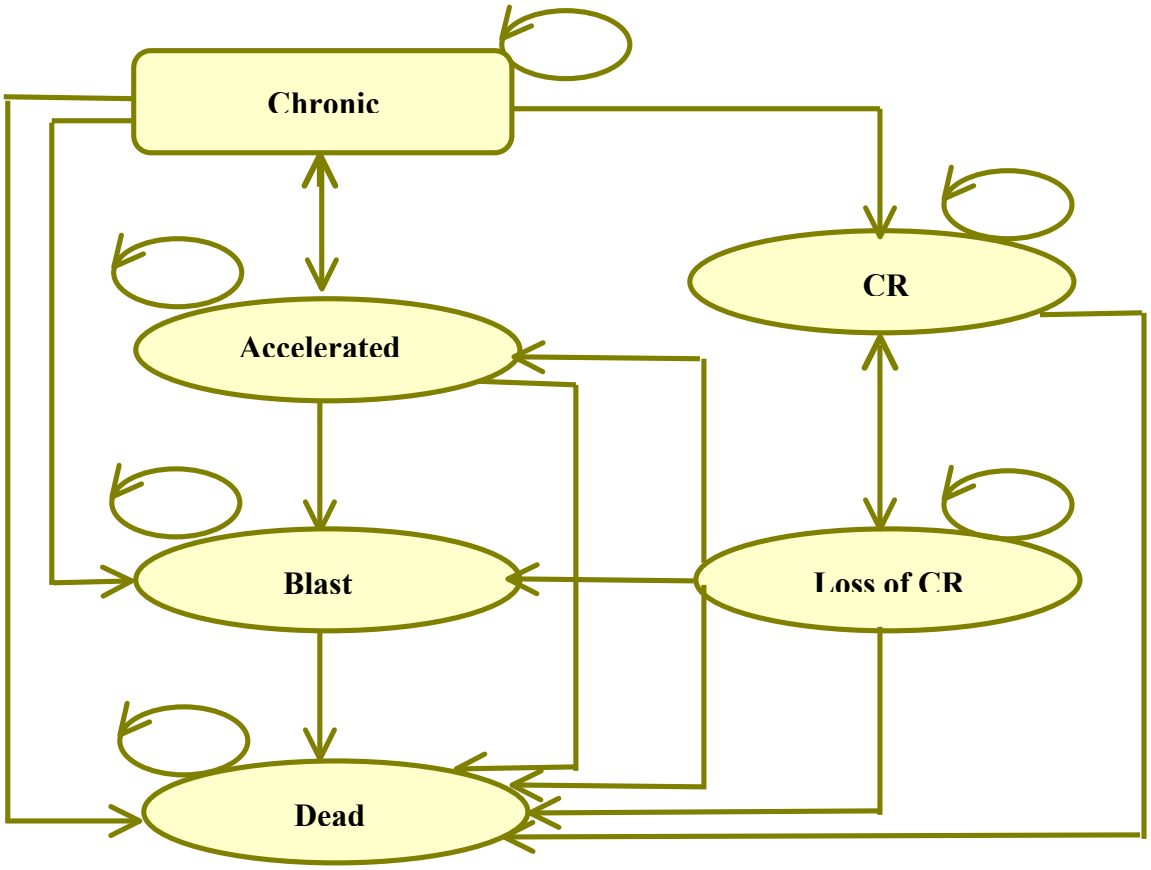
For patients in pathway 2, treatment starts as IFN-α and switches to imatinib on progression of loss of response. Progression rates from studies of imatinib as second line treatment are used for those who have lost a CR[59], and death rates calculated by applying a RR of survival estimated from Novartis Study 0106[60].

Patients on pathway 3 continue on hydroxyurea until blast phase, when they receive mercaptopurine.

Each cohort begins in the chronic state, and death is possible from all states. Disease progression is obtained from published progression curves and are partitioned in a ratio of 2:1 between progression to accelerated and blast phases (data from Novartis study 0106[60]).

Figure 2 shows the possible transitions between health states for patients receiving imatinib and IFN-α as first line treatments in the model (pathways 1 and 2). There are two additional states - cytogenetic response and loss of cytogenetic response. A person is permitted to move from chronic phase to all other states except loss of cytogenetic response.

Figure 2 Pathway for chronic phase CML patients treated with imatinib or interferon alpha



Costs

The costs of all the drug treatments were obtained from the British National Formulary (BNF 44, September 2002). Cost such as hospital outpatient visits, inpatient hospital stay, bone marrow tests, blood transfusions and radiology tests were also considered and were obtained from the Southampton University Hospitals NHS Trust (SUHT) databases. Inpatient and outpatient costs were the submitted reference costs for 2001 to 2002 and inpatient visits were assumed to be 3 days duration. Outpatient visits were assumed to be 50% initial and 50% follow up. All other costs were direct costs for 2002 to 2003. The cost of radiology tests was composed of one chest X-ray and one basic CT scan. The cost of a bone marrow transplant was composed of 20 units of full blood, 10 units of platelets and 2 hours nursing time (average of grade E and D). Management is predominantly outpatient in nature and is

likely to be very similar between treatments. The number of hospital visits and tests per cycle as used in the model were estimated by haematology consultants. Costs are discounted at 6% per year according to current National Institute for Clinical Excellence recommendations.

QALY calculations

Quality of life for those with CML varies with treatment and advancing disease. No empirical studies directly measuring utility values relating to CML were identified, other than the study submitted by Novartis. In the absence of population derived utilities, values from the Novartis study 0106[60] were used. These are patient estimates and to a large extent are likely to capture preference for the treatment as well as a preference for being in a particular health state. Sensitivity analyses using clinician derived estimates from the Novartis submission[60] were performed. QALYS are discounted at 1.5% per year in line with current National Institute for Clinical Excellence recommendations.

Modelling of survival data

Survival data were obtained from published studies of the effectiveness of various drug treatments for CML (see Section 4, page 36). We based the economic model on survival curves and progression curves.

The following transition probabilities were modelled as being cycle dependent (i.e. the transition probability changes as the time spent by the cohort in the model increases).

- Chronic to accelerated/ blast
- Chronic/ accelerated/ cytogenetic response to death
- Chronic to cytogenetic response

In order to obtain the transition probabilities we electronically scanned the survival curves and used the program TechDig to obtain coordinates for a number of points along the curve. These coordinates were used to estimate a Weibull distribution of the following formula:

$=EXP-\lambda*(time/year^{\gamma})$

λ and γ were estimated using a least squared method to achieve best fit with data taken from survival and progression curves. Transition probabilities were calculated from the cumulative survival function given a cycle length of three months.

The following transition probabilities were constant each cycle and were derived from the literature (for a description of values and studies see Table 28, page 67):

- Accelerated to blast
- Blast to death
- Chronic to cytogenetic response

When calculating the transition probabilities for imatinib as second line treatment, we used data from the published chronic phase 2 trial[59] for the first 5 cycles (1.25 years) after which we used the IFN-α data derived from the Italian trial[21] as a conservative estimate.

In order to estimate transition probabilities for HU as first line treatment we calculated a hazard ratio compared to IFN-α. The scanned survival or progression curves were compared

in Stata™, assuming an appropriate distribution (Weibull, gamma, exponential, or log normal) to estimate the hazard ratio and standard error. This was used as an estimate of the relative risk. Separate hazard ratios were calculated for mortality, progression and cytogenetic response. For imatinib, insufficient long-term data were available. A survival function was estimated from point data provided at 6, 9, 12, and 18 months from the Novartis study 0106,[60] and then a similar procedure as with HU was undertaken. It was not possible to estimate the standard error using the point data, so for survival a large standard error was assumed in order that the confidence interval crossed 1, to reflect the lack of statistical significance demonstrated so far. Sensitivity analyses were used to explore the effect of uncertainty around all parameters.

Calculation of incremental cost utility

For each treatment we calculated the total number of life-years gained, the QALYs gained (i.e. total summed quality of life associated with the numbers of people in each of the possible heath states per cycle), and the total costs (i.e. the total summed costs of treating each person in each health state per cycle). Each of these sets of three figures was summed over the total life of the model (20 years). The ICER was then calculated for each combination of treatments using the following formula:

=(total costs drug A – total costs drug B)/ (QALYS gained drug A- QALYs gained drug B)

Sensitivity analysis

There is uncertainty concerning many of the data incorporated in the economic model. Extensive one-way sensitivity analyses were performed. We modelled the following scenarios in sensitivity analysis:

- Using data from different studies for progression and survival with IFN-α
- Loss of CR or progression on imatinib leads to treatment with an increased dose of imatinib (600mg/day)
- Loss of CR or progression on imatinib leads to treatment with a combination of imatinib (400mg/day) and IFN-α (3MU), and an unchanged progression curve
- Loss of CR or progression on IFN-α leads to treatment with HU
- Pegylated IFN-α costs are used instead of IFN-α (with no difference in progression or survival)
- Using clinician derived set of utilities
- Assuming all relative risks of imatinib compared to IFN-α are 1

Probabilistic analysis

In addition, to estimate the effect of uncertainty in all parameters simultaneously, a probabilistic analysis was undertaken. Monte Carlo simulation was performed, with 1000 iterations. A graphical representation of uncertainty was generated on a cost-effectiveness plane. A cost-effectiveness acceptability curve was derived to show the probability that imatinib is more cost-effective than other treatments at a range of values that the NHS may be willing to pay per QALY gained.

3.2.3 Comparisons between independent economic analysis and industry submission

The results from the industry model and the independent economic evaluation were compared, and reasons for any differences explored.

4 EFFECTIVENESS

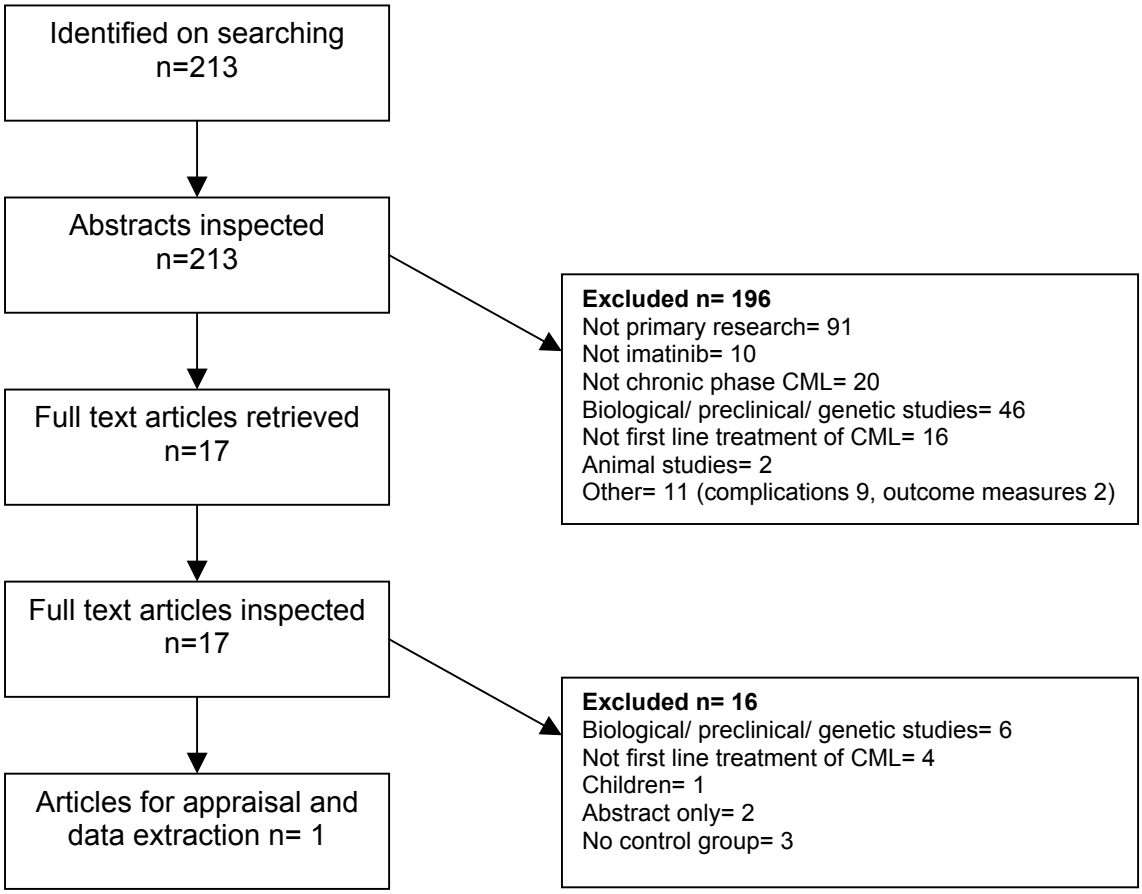
4.1 Research available

4.1.1 Imatinib

No studies of imatinib identified in the previous NICE assessment report were included in this report as they all considered second line treatment of CML.

The update search identified a total of 213 articles, one of which was included after completing the selection process (Figure 3). Twelve of the 213 articles identified were found through handsearching.

Figure 3 Flowchart demonstrating inclusion/ selection process for Imatinib



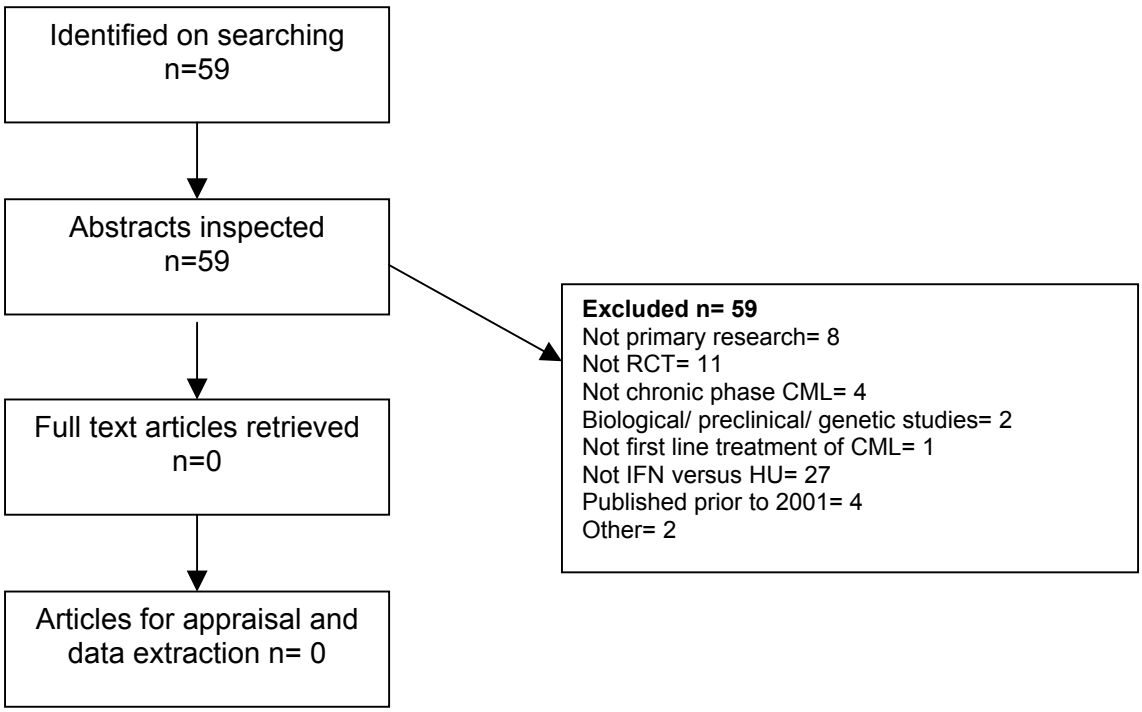
4.1.2 Interferon alpha compared to hydroxyurea

Four RCTs were included from the previous NICE assessment. Two of the RCTs from the previous assessment report were excluded as more than 25% of the control groups received

Busulphan.[61;62] In addition, the one published meta-analysis was excluded as more complete documentation of relevant outcomes were included in individual trial reports.[63]

The additional update search failed to identify any new relevant RCTs. The inclusion process for the update search is illustrated in Figure 4.

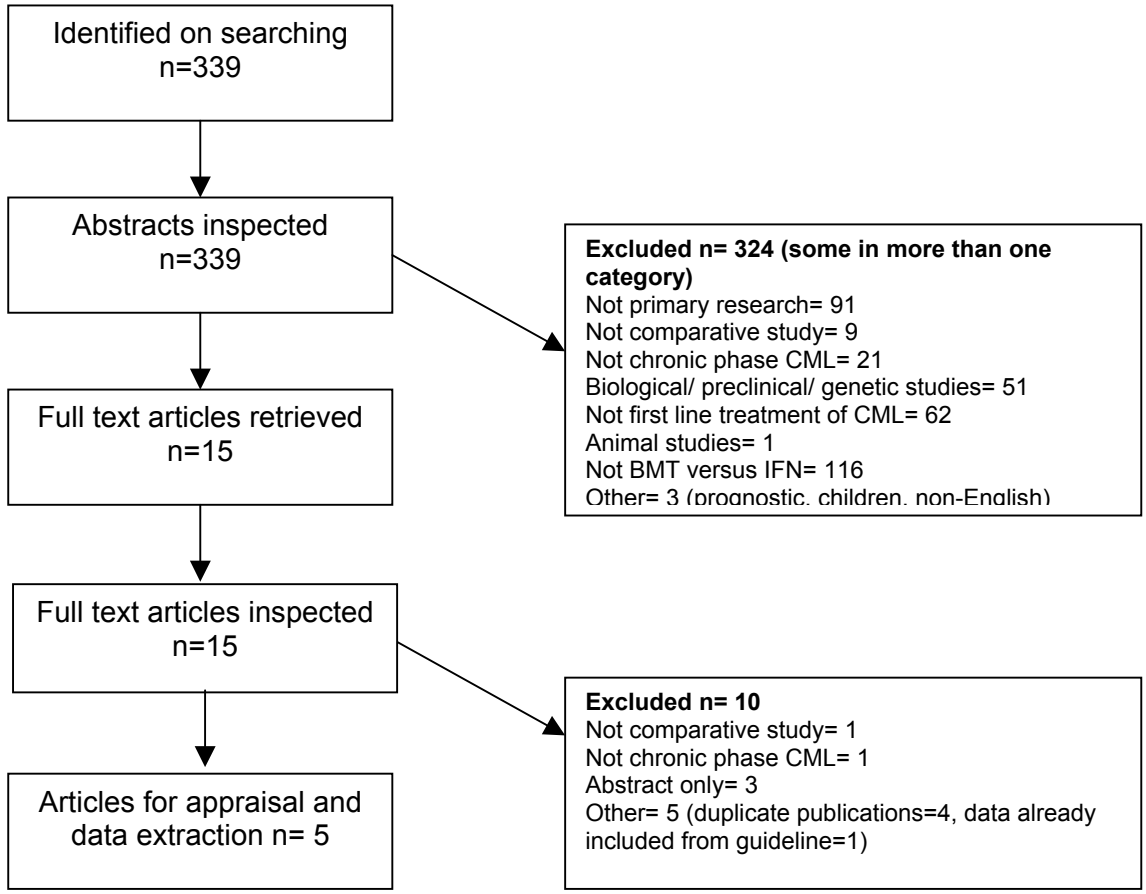
Figure 4 Flowchart demonstrating inclusion/ selection process for interferon alpha versus hydroxyurea (update search)



4.1.3 Interferon alpha compared to bone marrow transplant

We identified 339 articles comparing BMT and IFN-α of which five met the inclusion criteria (Figure 5).

Figure 5 Flowchart demonstrating inclusion/ selection process for interferon alpha versus bone marrow transplantation



A list of the full text articles inspected and excluded (along with reasons) is shown in Appendix 10.4 (page 93).

Table 5 Number and type of studies included

Intervention and comparison	Systematic reviews	RCTs	Non-randomised comparative studies
IFN-α versus Imatinib	0	1	0
IFN-α versus HU	0	4	-*
IFN-α versus BMT	0	0	5

*Study design was excluded for this comparison

4.2 Imatinib versus interferon alpha plus Ara-C

4.2.1 Quality of study

The included study[60] is referred to as study 0106 and was performed by Novartis. It is also referred to as the International Randomised Study of Interferon + Ara-C vs. STI571 in CML (IRIS). Subsequent to the literature search it has been published with updated data.[64] The study randomised a total of 1106 people to treatment with either imatinib or IFN-α+Ara-C. The study enrolled people between June 2000 and February 2002. The median age of participants was 51 years and median length of follow-up was 13-14 months.

The quality of the included study (Novartis study 0106[60]) is shown in Table 6. Novartis performed the day-to-day management of the trial, held the database and performed the statistical analysis. An external steering group monitored trial progress and quality control measures were implemented. There is the possibility of bias due to undisclosed data

Table 6 Summary of the quality of the included study comparing imatinib to interferon alpha

Quality criteria	
Proper randomisation?	?
Adequate concealment?	✔
Groups similar at baseline?	✔
Eligibility criteria stated?	✔
Outcome assessors blinded?	X
Providers of care blinded?	X
Patients blinded?	X
Point estimates and measures of variability?	✔
Power calculation performed at study design?	✔
All patients accounted for?	✔
Analysis performed on ITT?	✔

✔ =yes, x=no, ?=not reported

Internal validity

Sample size

The study randomised 553 people to receive imatinib and 553 to receive IFN-α+Ara-C. A sample size calculation was performed prior to commencing the study. The original protocol sample size calculation was based on a difference in time to treatment failure (median of 4.8 years on imatinib compared to 3.6 years on IFN-α+Ara-C) which resulted in a total sample size of 351 patients per treatment arm with allowance for 17.5% drop-out (total sample size 850).

An amendment was made to the protocol which changed the primary outcome measure to time to progression (with 5-year progression free rate on the control arm expected to be 50%). The amended sample size calculation was performed: based on a hazard ratio of 0.75 for imatinib compared to IFN-α+Ara-C, which translates into progression free survival of 50% in IFN-α+Ara-C arm compared to 60% in imatinib arm approximately 822 patients needed to be recruited with an allowance for a drop-out of 10% per year (total of 1032 patients).

This was also considered to be sufficient power for the secondary outcome measure which was changed, in an amendment to the original protocol, to major CR. There was sufficient power to detect a 10% increase in major CR for imatinib compared to IFN-α+Ara-C (assumed to be 41%).

Selection bias

Randomisation was performed at a central office. Staff members in each participating unit were required to call the number of an automated voice response system to request treatment assignment. The method used to generate the random sequences was not reported, and randomisation was stratified by country. No details are provided to indicate how many people were screened in each centre before randomisation, but an average of between 5 and 6 people were recruited per centre. No post randomisation exclusions are reported in the intention-to-treat analysis although 2 people in the imatinib group and 20 in the IFN-α+Ara-C group never started treatment.

The imatinib and IFN-α+Ara-C groups were essentially similar at baseline for age, gender, weight, ECOG status, previous treatment with HU and Sokal scores.

Performance bias

Performance bias refers to systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation. The study was "open label". IFN-α was administered subcutaneously whereas imatinib was taken orally. Concurrent treatments may have differed between treatment groups but are not detailed.

Detection bias

Detection bias refers to systematic differences between comparison groups in how outcomes are ascertained, diagnosed or verified.

It is unlikely that there were systematic differences in how the objective study outcomes were measured between the two treatment groups. Detailed assessment schedules were part of the trial protocol. Outcome assessors and providers of care and patients were not blinded. There is a possibility of detection bias for the subjective outcome measures such as quality of life and treatment intolerance.

Outcomes may have been influenced by desire to cross over to the alternative treatment group (especially for the initial IFN-α+Ara-C arm). Quality of life assessment and intolerance to the treatment were assessed at the time the patient crossed over. If patients thought that a poor result would assist them in crossing over then a bias may have been present. It is also possible that if healthcare professionals felt it was in the best interest of the patient to cross over, their assessment of outcomes might have differed in comparison to patients on the alternative treatment. Any bias of this nature is likely to have favoured imatinib.

Attrition bias

Attrition bias refers to systematic differences between comparison groups in withdrawals or exclusions of participants from the results of a study.

All people who were enrolled in the trial were accounted for. In the imatinib grou,p 51/553 (9%) discontinued treatment compared to 170/553 (31%) in the IFN-α+Ara-C group. The reasons for treatment discontinuation are shown in Table 7. The main reason for the difference in discontinuation was withdrawal of consent in the IFN-α+Ara-C group. Those who discontinued treatment were given a final study visit and evaluation. People discontinuing due to adverse events were followed weekly for 4 weeks or until resolution of

the adverse event. Survival of all patients who discontinued treatment is planned for 8 years.

There is likely to be a systematic difference between the people who discontinue in the two groups

In addition 7/553 (1%) people in the imatinib group crossed over treatment compared to 218/553 (39%) in the IFN-α+Ara-C group. The reasons for crossing over to the other treatment arm are shown in Table 8. The main reason for the difference in cross over rates was intolerance of treatment. Note that patient request to cross over was allowed by amendment three to the trial protocol. In addition there were incentives for institutions to cross patients over to treatment with imatinib, as imatinib was funded by the pharmaceutical company whereas IFN-α+Ara-C was provided within healthcare budgets.

Table 7 Reasons for discontinuation of treatment in Study 0106.

	Novartis study 0106[60]	
	Imatinib (n=553)	**IFN-α+Ara-C (n=553)**
Adverse reactions	11 (2%)	31 (6%)
BMT	5 (0.9%)	7 (1%)
Refusal/ voluntary withdrawal	10 (2%)	74 (13%)
Protocol violations	10 (2%)	15 (3%)
Loss of contact with patient	2 (0.4%)	6 (1%)
Therapeutic inefficiency/ resistance	9 (2%)	29 (5%)
Administrative problems	0	6 (1%)
Death	4 (0.7%)	2 (0.4%)
Total	**51 (9%)**	**170 (31%)**

Table 8 Reasons for crossing over to the other treatment arm

	Novartis study 0106[60]	
	Imatinib (n=553)	**IFN-α+Ara-C (n=553)**
Intolerance of treatment	4 (0.7%)	126 (23%)
No complete HR at 6 months*	0	41 (7%)
No major CR at 12 months†	0	1 (0.2%)
No major CR at 24 months	0	1 (0.2%)
Increase in WBC count	2 (0.4%)	25 (5%)
Loss of complete HR	0	20 (4%)
Loss of major CR	1 (0.2%)	4 (0.7%)
Total	**7 (1%)**	**218 (39%)**

*only prior to protocol amendment (Nov 2000), † changed to 24 months in protocol amendment (Jan2002)

The high discontinuation rate (31%) combined with the high cross over rate (39%) in the IFN-α+Ara-C group give a combined attrition rate of 70% for that group (median follow-up of 13 months). The study is therefore highly prone to attrition bias, as those who dropped out of the study may have differed from those who remained. Due to the high rates of attrition and crossover, performing analyses on an intention-to-treat basis is important. The study did perform intention-to-treat analyses in which all people randomised to IFN-α+Ara-C were analysed in that group regardless of whether they had crossed over treatment. Any attrition bais is likely to favour the IFN-α+Ara-C group. However, as response to IFN-α+Ara-C is slower than to imatinib, and 91% of cross overs were within the first year, some responses after crossover might still be attributable to IFN-α+Ara-C.

Minor discrepancies were noted in the numbers reported – only seven patients are reported as crossing over from imatinib to IFN-α+Ara-C, but 17 are reported as discontinuing second line treatment with IFN-α+Ara-C (i.e. must have crossed over from imatinib).

In the original protocol, the primary end-point, was time to progression and was defined as:

-**failure**: death due to any cause, progression to accelerated or blast phase, loss of major CR, loss of HR, increase in white blood count (as a reason for cross-over), discontinued due to reasons other than progression or death.

-censored: cross-over due to reasons other than progression, or still on treatment without progression.

The primary end-point was changed during the study. Patients discontinuing treatment were censored, as opposed to failing. This is likely to favour the IFN-α+Ara-C arm but may be a form of informative censoring i.e. there may be a relationship between those censored and the outcome. This leads to further possibilities of bias.

Reporting bias

The study did report point estimates as well as measures of variability (confidence intervals for survival estimates). A number of analyses were performed including first line treatment and per protocol analyses. These are not presented here; the intention-to-treat analysis is more conservative but less biased.

External validity

The study provided sufficient details to make an assessment of generalisability. Eligibility and exclusion criteria were described. Patient details such as age, sex and risk scores were provided. Patients were recruited from a number of different countries, predominantly the United States.

The patients in this study had generally less severe disease than those enrolled in the studies comparing IFN-α and HU (see Appendix 10.7.2, page 12). The results are likely to be generalisable to a less severe population than would be seen in clinical practice (Table 9).

Table 9 Comparison of Sokal score low risk groups (imatinib and IFN-α studies)

Study (treatment)	% Sokal low risk group
Novartis study 0106[60] (imatinib)	50.4%
Benelux (IFN-α)[5]	29%
Broustet (IFN-α)[6]	29.2%
Hehlmann (IFN-α)[7]	27.1%

4.2.2 Patient characteristics

Patient characteristics and treatment details are summarised in Table 10.

Table 10 Patient characteristics and treatment details

Study characteristic	Imatinib	IFN-α+Ara-C	Total
Median haemoglobin level g/dl (range)	12.3 (4.3-21.9)	12.2 (4.2-16.8)	12.3 (4.2-21.9)
Median WBC 10^9/L (range)	95 (4-537)	85 (3-1082)	90 (3-1028)
Splenomegaly (any)	23%	27%	25%
Hepatomegaly (any)	10%	8%	9%
Extramedullary involvement	27%	31%	29%
Median age (minimum-maximum)	50 (18-70)	51 (18-70)	51 (18-70)
Sex ratio male:female (% male)	342:211 (62)	310:243 (56)	652:454 (59)
Time since diagnosis	Median 2.14 months	Median 1.77 months	Median 1.97 months
Sokal score	Low 53% Int 29% High 19%	Low 48% Int 30% High 22%	Low 50% Int 29% High 21%
Previous treatment Anagrelide permitted	HU 88%	HU 85%	HU 87%
Concomitant drugs	HU, leukopheresis, allopurinol and anagrelide permitted	HU, leukopheresis, allopurinol and anagrelide permitted	HU, leukopheresis, allopurinol and anagrelide permitted
Median length of follow-up	14 months	13 months	?

The type of IFN used was IFNαsc, with a target dose of 5MU/m2/day

4.2.3 Study results

The primary end-point was time to progression. Secondary endpoints were survival and quality of life. Table 11 reports the main results in the intention-to-treat analysis.

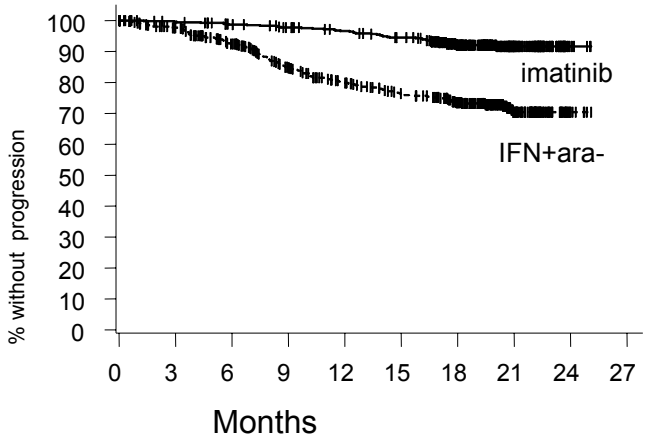
Table 11 Main results from Imatinib versus IFN-α+Ara-C trial

Treatment	Imatinib	IFN-α+Ara-C	P value
Total number of people progressing	24/553 (4.3%)	103/553 (18.6%)	<0.001*
Overall survival (%)	542/553 (98.0)	533/553 (96.4)	NS
Complete HR (%)	523/553 (94.6) (95%CI 92.3-96.3)	423/553 (76.5) (95%CI 72.7-80.0)	<0.001
Partial HR (%)	Not reported	Not reported	
Major HR (%)	Not reported	Not reported	
Complete CR (%)	375/553 (67.8)	110/553 (19.9)	<0.001*
Partial CR (%)	82/553 (14.8)	110/553 (19.9)	0.03*
Major CR (%)	457/553 (82.6) (95%CI 79.2-85.7%)	220/553 (39.8) (95%CI 35.7-44)	<0.001
Withdrawal due to side effects	11/553 (2.0)	31/553 (5.6)	0.002*
Cross over due to intolerance	4/553 (0.7)	126/553 (22.8)	<0.001*

*calculated by the authors of this assessment from reported figures.
IFN-α+Ara-C= interferon alpha plus cytarabine, HR= haematological response, CR= cytogenetic response

Figure 6 shows a Kaplan-Meier estimate of those people on imatinib compared to IFN-α+Ara-C who did not die, progress to accelerated or blast phases, lose a response or show an increased WBC count. A greater proportion of patients treated with imatinib did not experience progression as defined above compared to those receiving IFN-α+Ara-C (p<0.001).

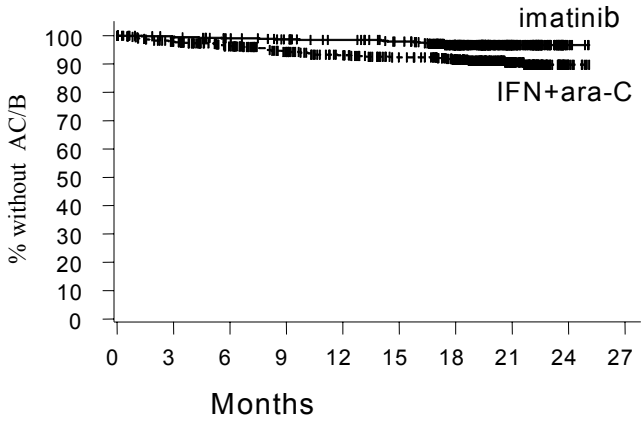
Figure 6 Time to progression for imatinib compared to interferon alpha plus Ara-C



(Source: data derived from personal communication, O'Brien)

At 12 month follow-up, the Kaplan Meier estimated proportion of patients who have not progressed to accelerated or blast phases is 98.5% with imatinib (based on 8 events) compared to 93.1% with IFN-α+Ara-C (based on 33 events), p<0.001(Figure 7).

Figure 7 Proportion of patients not progressing to accelerated or blast phases with imatinib compared to interferon alpha plus Ara-C



(Source: data derived from personal communication, O'Brien)

4.2.4 Quality of life

All patients included in the study were assessed for quality of life (QoL) except Danish participants and Flemish speaking patients in Belgium. A total of 1067 people were included. Quality of life was assessed in included patients at baseline, monthly for six months, then at the end of 9, 12, 18 and 24 months. Quality of life assessment also occurred when a patient crossed over to the other treatment. The following instruments were used to assess quality of life: Functional Assessment of Cancer Therapy- Biological Response Modifier (FACT-BRM), Global Rating of Change (GRC) Scale and the EQ-5D. The primary quality of life outcome was the Trial Outcome Index using four domains of the FACT-BRM – physical well being, functional well being, two treatment specific scales, physical and emotional.

A brief assessment of the quality of life evaluation is presented in Appendix 10.5. (page 96). Criteria were taken from a systematic review by Clark and colleagues.[65] Overall, the FACT-BRM appears to be reliable and valid, although only 4 of the 6 subscales were used in the Trial Outcome Index. Interpretation is hampered by differential completion rates in the two groups, 80% at 12 months in the imatinib group and 59% in the IFN-α+Ara-C group. There were also a large number of withdrawals in the IFN-α+Ara-C arm.

An additional concern is whether patients knew that their rating of QoL may affect their ability to be able to cross over to the alternative treatment. There is, therefore, a possibility of responder bias although there is no evidence whether or not this occurred. The analysis appears to impute missing values through a pattern mixture technique. Analysis of raw scores reveals a similar pattern to the adjusted scores, although absolute values are slightly higher.

Table 12 summarises the quality of life data from the Trial Outcome Index, analysed on an intention-to-treat basis.

Table 12 Quality of life results for the Trial Outcome Index

Time of assessment	Imatinib (n=533)	IFN-α+Ara-C (n=534)	P value
Baseline mean (se)	83.6 ±10.5	81.4 ±1.1	<0.068
Month 1 mean (se)	84.2 ±1.1	64.6 ±1.1	<0.0001
Month 2 mean (se)	85.4 ±1.0	63.6 ±1.0	<0.0001
Month 3 mean (se)	86.4 ±1.0	66.1 ±1.2	<0.0001
Month 4 mean (se)	86.9 ±1.1	67.6 ±1.2	<0.0001
Month 5 mean (se)	86.8 ±1.1	68.1 ±1.3	<0.0001
Month 6 mean (se)	86.6 ±1.2	68.6 ±1.4	<0.0001
Month 9 mean (se)	87.0 ±1.3	71.8 ±1.7	<0.0001
Month 12 mean (se)	87.2 ±0.9	78.0 ±1.5	<0.0001

The small non-significant difference at baseline favours imatinib. Better QoL scores were found with imatinib than IFN-α+Ara-C at each subsequent assessment point. Quality of life scores increased with time in both study groups. The difference between the two groups was greatest at month 2, and least at month 12. The increase in the IFN-α+Ara-C group may be partly accounted for by crossover to imatinib.

The Global Rating of Change scale was used to validate (as a supplementary measure) the Trial Outcome Index on a subset of 200 people in the United States. Results are shown in Table 13. Note that not all patients completed each assessment.

Table 13 Global Rating of Change scale scores (ITT analysis)

Baseline to month 1	Imatinib (%)	IFN-α+Ara-C (%)
Number of patients	84	90
A lot better	15 (18)	4 (4)
Somewhat better	22 (26)	7 (8)
About the same	38 (45)	27 (30)
Somewhat worse	9 (11)	34 (38)
A lot worse	0	18 (20)
Month 2 to month 3		
Number of patients	94	100
A lot better	19 (20)	11 (11)
Somewhat better	23 (24)	11 (11)
About the same	48 (51)	49 (49)
Somewhat worse	4 (4)	25 (25)
A lot worse	0	4 (4)
Month 5 to month 6		
Number of patients	94	82
A lot better	11 (12)	14 (17)
Somewhat better	20 (21)	16 (20)
About the same	52 (55)	40 (49)
Somewhat worse	10 (11)	10 (12)
A lot worse	1 (1)	2 (2)

From baseline to month 1 of treatment the IFN-α+Ara-C patients most reported being the same or worse, where as the imatinib patients mostly reported being the same or better. By month 5-6 equivalent numbers of people in each group reported feeling better; however, a proportion of those (32%) in the IFN-α+Ara-C group had crossed over to imatinib by then.

4.2.5 Adverse effects

Adverse events were reported for the study population who received at least one dose of study medication (imatinib n=551 and IFN-α+Ara-C n=533). Firstly, the most frequently reported adverse events classified by system organ class are shown (Table 14). Only adverse events that affected more than 15% of either treatment group are included. Total percentages are presented along with the proportion of people experiencing grade 3 and 4 adverse events.

Table 14 Most frequently reported adverse events by organ system (affecting more than 15% of people)

	All grades		Grades 3/4	
System organ class	**Imatinib (%)**	**IFN-α+Ara-C (%)**	**Imatinib (%)**	**IFN-α+Ara-C (%)**
Eye disorders	30.1	21.2	1.3	2.4
Gastrointestinal disorders	73.3	82.6	6.0	14.8
General disorders	59.3	91.9	3.3	35.3
Infections and infestations	55.2	46.3	3.6	5.1
Investigations	24.7	34.1	4.4	6.6
Metabolic and nutritional disorders	18.0	45.2	1.6	3.8
Musculoskeletal disorders	71.0	74.9	6.5	17.8
Nervous system disorders	46.3	68.7	3.4	16.5
Psychiatric disorders	25.2	57.8	0.9	17.3
Respiratory/ thoracic disorders	40.5	49.7	2.0	4.9
Skin and subcutaneous disorders	60.8	63.2	2.9	3.9
Vascular disorders	11.3	17.3	1.8	2.6
Any event	**98.0**	**99.6**	**41.0**	**75.0**

Both treatments were associated with high numbers of adverse events, with nearly all patients experiencing an event within the trial period. In general, IFN-α+Ara-C was associated with a more adverse events and with more serious adverse events. The most common adverse events associated with imatinib treatment were gastrointestinal, musculoskeletal and skin. For IFN-α+Ara-C the most common adverse events were general, gastrointestinal and musculoskeletal.

Table 15 summarises adverse events in more detail, according to their preferred term. All adverse events are reported that affected more than 10% of either group. Total percentages are presented along with the numbers experiencing grade 3 and 4 events.

Table 15 Adverse events according to preferred terms affecting at least 10% of people.

	All grades		Grades 3/4	
Adverse events	**Imatinib (%)**	**IFN-α+Ara-C (%)**	**Imatinib (%)**	**IFN-α+Ara-C (%)**
Nausea	42.5	60.8	0.4	5.1
Muscle cramps	33.4	8.6	0.7	0.2
Fatigue	30.7	64.7	1.1	24.0
Diarrhoea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Arthralgia	26.3	38.3	2.2	6.8
Periorbital oedema	25.8	1.1	0.2	0
Myalgia	20.7	38.5	1.5	7.7
Rash	19.8	14.4	1.3	1.1
Nasopharyngitis	19.2	7.7	0	0.2
Oedema peripheral	15.8	3.9	0.2	0
Dyspepsia	15.1	9.0	0	0.8
Pain in limb	14.7	15.0	1.1	2.6
Vomiting	14.7	26.6	0.9	3.4
Back pain	14.5	18.6	0.9	2.4
Pharyngolaryngeal pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper respiratory tract infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight increased	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3
Abdominal pain	10.3	10.3	1.1	1.9
Abdominal pain upper	9.6	12.2	0.5	1.5
Depression	8.9	34.7	0.5	12.4
Bone pain	8.0	14.6	0.9	3.0
Constipation	7.6	13.9	0.7	0.2
Rigors	6.9	33.8	0	0.8
Anxiety	6.5	10.9	0.2	2.6
Dyspnea	6.5	14.4	1.3	1.7
Pruritus	6.5	11.3	0.2	0.2
Influenza like illness	6.4	18.4	0	1.1
Night sweats	6.4	15.0	0.2	0.4
Anorexia	4.7	31.3	0	2.4
Sweating increased	3.3	14.4	0	0.4
Alopecia	2.2	14.6	0	0.2
Weight decreased	2.2	16.9	0	1.1
Asthenia	1.6	10.9	0	1.9
Dry mouth	1.6	10.3	0	0.2
Mucosal inflammation	0.7	10.1	0	3.2

It can be seen that imatinib and IFN-α+Ara-C have different side-effect profiles. Imatinib is associated with more of the following kinds of adverse events than IFN-α+Ara-C: muscle cramps, periorbital oedema, rash, nasopharyngitis, oedema peripheral, dyspepsia, pharyngolaryngeal pain, upper respiratory tract infection and weight increase. However, all the other adverse effects are more common with IFN-α+Ara-C. Note that IFN-α alone has fewer adverse effects than the combination with Ara-C.

Dose changes, for whatever reason, occurred at different rates in each group with 87% of the IFN-α+Ara-C group having their initial dose changed compared to 45% of the imatinib

group. It is reported that there were six deaths thought to be unrelated to CML in the imatinib arm and seven in the IFN-α+Ara-C arm. In addition, there have been a number of independent case reports recently published on the side-effects of Imatinib for CML. A summary of these studies is presented in Table 16.

Table 16 Summary of literature on side effects of Imatinib.

Author/ Year	Study design	Type of side effect	Number of people reported with side effect
Etienne *et al.*, 2002[66]	Case series (n=133)	Repigmentation of grey hair	9/133 (occurring after median of 5 months treatment)
Drummond *et al.*, 2002[67]	Case series (n=82)	Rashes *Patient number* 1= eczematous eruptions, grade 2 2= eczematous eruptions, grade 2 3= (eczematous eruptions, grade 2) 4= eczematous eruptions, grade 2 5= eczematous eruptions, grade 2 6= eczematous rash on face and limbs then on rechallenge generalised exfoliate dermatitis 7= Biopsy proven small vessel skin vasculitis 8= erythema nodosum	8/82 (10%) *Patient number* 1= rash resolved, continued IM 2= rash resolved, continued IM 3= antihistamine treatment 4= steroid cream treatment 5= oral prednisolone (8 weeks) 6= discontinued Imatinib 7=oral prednisolone (4 months) 8= oral prednisolone plus azathioprine, discontinued Imatinib
Milojkovic *et al.*, 2002[68]	Case series (n=41)	Grade 1-IV dermatosis (including one case of severe dose-limiting erythroderma)	11/41
Ebnoether *et al.*, 2002[69]	Case reports (n=2, 61 year old female & 68 year old male)	Massive cerebral oedema	2
Barton *et al.*, 2002[70]	Case report- 51 year old male	Cardiac tamponade, oedema, weight gain, effusions and ascites	1
Vidal *et al.*, 2002[71]	Case report- 58 year old male	Imatinib-induced Stevens-Johnson syndrome (severe allergic reaction)	1
Lim &Muir, 2002[72;73]	Case report	Erosive oral lichenoid reaction to Imatinib	1
Esmaeli *et al.*, 2002[74]	Case report- 63 year old male	Severe periorbital oedema	1
Konstantopoulos *et al.*, 2002[75]	Case report- 42 year old female	Pityriasis rosea skin eruptions	1
Brouard & Saurat, 2001[76]	Case report	Severe adverse cutaneous reaction (acute generalised exanthematous pustulosis)	1
Ohyashiki *et al.*, 2002[77]	Case report- 56 year old female	Focal necrosis resembling acute viral hepatitis	1

A total of 37 people were affected. Of these 37 reports of adverse events, 25 (68%) were for adverse events that were listed as some of the most commonly reported in Table 16. These reports confirm oedema and skin reactions as serious potential adverse events associated with imatinib.

4.2.6 Research in progress

The search strategy identified three studies that are currently in progress (Table 17). These will help fill gaps in the current evidence base for Imatinib and will help resolve some of the current uncertainties. No trials comparing imatinib to BMT are yet in progress.

Table 17 Studies of imatinib currently in progress

Study/ question	Lead investigator	Organisation	Expected completion date	Study Design	Patients	Methodology
A multi-centre phase I/II study to determine the safety, tolerability and efficacy of PEG Interferon (PEG Intron) in combination with ST1571 (imatinib) in patients with chronic phase chronic myeloid leukaemia (PISCES)	Dr S O'Brien	Royal Victoria Infirmary, Newcastle, UK	2003	Case series	Chronic phase CML, aged 2-18 years	Study will follow a dose escalation schedule to define the maximum tolerated dose of both PEG interferon and imatinib. Safety and survival will be collected for 2 years.
A Phase 1 Pilot, Open-labelled, Single-centre Multiple Ascending Dose Study to Evaluate the Pharmacokinetics and Safety of Administration of STI-571 in Patients with Haematological Malignancies Undergoing an Allogeneic Stem Cell Transplant.	Professor Ray Powles	The Royal Marsden NHS Trust, Surrey	01/03/2001	Case series	Patients with haemato-logical malignancies undergoing allogenic stem cell transplantation	Dose finding study
STI571 Prospective International Randomized Trial (SPIRIT)	B Druker. Guilhot F O'Brien S	Portland, Oregon USA Poitiers, France Newcastle, UK (Multicentre)	Not stated, Study still awaiting funding in the UK	Phase III, multicenter, open-label, prospective randomized trial	Patients must be newly diagnosed CML (<3 months) and have been treated with only hydroxyurea and/or anagrelide.	Study compares imatinib alone at 400 versus 600 mg versus imatinib plus cytarabine (Ara-C) versus imatinib plus interferon-alpha in patients with chronic phase CML.

4.3 Interferon alpha versus hydroxyurea

4.3.1 Quality of studies

The four included studies were all randomised controlled trials. They each compared treatment with IFN-α to HU and enrolled between 58 and 326 people. The median age of participants ranged from 47-59 years and the longest period of follow-up was a median of 112 months.

The quality of the four included RCTs is detailed in Appendix 10.7 (page 109). Overall, the studies were of reasonable quality. The main potential sources of bias were lack of blinding and allocation concealment.

4.3.2 Study and patient characteristics

The four included studies were published between 1991 and 1998. They enrolled a total of 902 patients. Studies were conducted in France, Germany Italy and Belgium/The Netherlands/Luxembourg. Median length of follow-up was 51 months in the Benelux study (1998)[5] and 112 months in the Italian study (1998). [21] Length of follow-up was not stated in the Broustet trial (1991)[6] and was 3 years after the last patient was randomised in the study by Hehlmann and colleagues (1994).[78]. Patient characteristics and treatment details are presented in more detail in Appendix 10.7.2 (page 112).

Compared to the Novartis study 0106[60] (imatinib versus IFN-α+Ara-C), the patients in these trials appear to have slightly more severe disease.

4.3.3 Study results

Median one year survival across the four studies was 96% (range 95-98%) for IFN-α compared to 96% (range 96-97%) for HU (Table 18). The median percentage of patients having a complete haematological response was 47% (range 31-62%) for IFN-α compared to 41% (range 39-42%) for HU. Median complete cytogenetic response was 6% (range 4-9%) for IFN-α and 0 (range 0-1%) for HU. The median percentage of people withdrawing due to side-effects was 24% (range 18-25%) for IFN-α compared to 4% (1-4%) for HU.

Table 18 Main results from interferon alpha versus hydroxyurea trials

Study	Benelux, 1998[5]		Broustet, 1991[6]		Hehlmann, 1994[78]		The Italian Cooperative Study Group on CML, 1998[21]		Median (range) Overall	
Treatment	**IFN-α**	**HU**	**IFN-α**	**HU**	**IFN-α**	**HU/BU**	**IFN-α**	**HU**	**IFN-α**	**HU**
Median survival	61 months	66 months	-	-	66 months	56.2 months	76 months (95% CI 69 to 86)	52 months (95%CI 43 to 66) p=0.002	66	56.2
1-year survival (%)	98	97	-	-	95	96	96	96	96 (95-98)	96 (96-97)
Complete HR (%)	62	42	-	-	-	-	31	39	47 (31-62)	41 (39-42)
Partial HR (%)	-	-	67	88	-	-	52	51	60 (52-67)	70 (51-88)
Major HR (%)	-	-	-	-	0	0	83	90	42 (0-83)	45 (0-90)
Complete CR (%)	9	0	7	0	4	0	5	1	6 (4-9)	0 (0-1)
Partial CR (%)	7	2	46	31	2	1	2	1	5 (2-46)	2 (1-31)
Major CR (%)	16	2	53	31	6	1	7	2	12 (6-53)	2 (1-31)
Withdrawal due to side effects	24	4	25	4	18	-	24	1	24 (18-25)	4 (1-4)

IFN-α= interferon alpha, HU=hydroxyurea, BU=busulphan, HR= haematological response, CR= cytogenetic response

Results are discussed in more detail and survival curves are presented in Appendix 10.7.3 (page 112).

4.3.4 Adverse effects

In general, more adverse effects were reported for IFN-α than HU treatment. The only adverse effects reported for HU were fatigue/ fever/ pain/ headache, renal including vasculitis, drug eruption and general intolerance. A wider variety of adverse effects were reported for IFN-α, with the most common including fatigue/ fever/ pain/ headache, neurological, psychiatric, anorexia/ nausea/ diarrhoea and thyroid insufficiency (See Appendix 10.7.4 (page 116).

Median withdrawal due to side-effects across the four studies was 24% (range 18-25) for IFN-α compared to 4% (range 1-4) for HU. For IFN-α this is a slightly lower percentage than those who withdrew or crossed over for intolerance (29%) in the Novartis study 0106.[60]

4.4 Interferon alpha versus bone marrow transplant

4.4.1 Quality of studies

The five included studies all compared BMT to IFN-α although none were randomised. They enrolled between 89 and 840 people. The median age of participants ranged from 31 to 35 in the BMT groups and from 41 to 54 in the IFN-α groups. The longest period of follow-up for the IFN-α groups was a median of 78 months (median length of follow-up not stated for the BMT groups).

The quality of the included studies is detailed in Appendix 10.8.1 (page 117). Overall, the studies were of variable quality with the main potential biases being lack of randomisation, groups dissimilar at baseline, lack of blinding and potential lack of study power.

4.4.2 Study and patient characteristics

The five included studies were published between 1998 and 2002. Two studies[11;12] enrolled patients prospectively and concurrently. The other three studies appear to be retrospective comparisons of patients based on available databases.[9;10;79] The studies were conducted in Italy (2), Japan (2) and the final study was multicentre and international. Length of follow-up was not stated in the Italian Cooperative Study, [79] and was only stated for the IFN-α group in the studies by Ohnishi (2000 and 2001)[11;12] and Gaziev and colleagues.[10] These three studies reported follow-up lengths for IFN-α of 54 months (range 30 to 76), 38 months (range 9 to 66) and 46.8 months (range 12 to 144) respectively. Gale and colleagues[9] reported average follow-up of 51.6 months for the BMT group and 78 months for the IFN-α group.

Patient characteristics are summarised in Appendix 10.8.2 (page 120). The median age in the IFN-α treatment arms ranged from 41 to 54 compared to 31 to 36 for the BMT treatment arms. In four of the five included studies, patients receiving drug therapy were newly diagnosed, whereas patients receiving BMT did so on average 9 to 29 months after registration in the trial. This is likely to bias against BMT in the survival analyses.

Treatment details are summarised in Appendix 10.8.3 (page 122). The type of BMT varied between studies and included HLA-identical sibling donors, identical twins, HLA-identical relatives and HLA-matched unrelated donors.

4.4.3 Study results

Four out of the five studies showed a long-term survival advantage for BMT compared to IFN-α, but a short-term (0-4 years approximately) disadvantage (Table 19). Median survival had not yet been reached in four studies and was not reported in the other study.

Table 19 Main results from bone marrow transplant versus interferon alpha studies

Study	Gaziev *et al.*, 2002[10]		Ohnishi *et al.*, 2001[12]		Ohnishi *et al.*, 2000[11]		Italian Cooperative, 1999[79]		Gale *et al.*, 1998[9]	
Treatment	**BMT**	**IFN-α**	**BMT**	**IFN-α**	**BMT**	**IFN-α**	**BMT**	**IFN-α**	**BMT**	**IFN-α**
Median survival	Not reached	7 years			**Related donor** Not reached in 6 years **Unrelated donor** approx 4.4 years	Not reached in 6 years	Not reached in 10 years	**HU/ BU** 4.5 years **IFN-α** *6* years	Not reached in 8 years	Approx 5.2 years (adjusted)
1-year survival rate (%)									84% (adjusted)	96% (adjusted)
5-year survival rate (%)			Predicted **Related donors** 72% **Unrelated donors** 67%	Predicted 79%	Predicted **Related donor** 93.3% **Unrelated donor** 21.9%	Approx 61%	Approx 65%	**HU/ BU** approx 45% **IFN-α** approx 58%		
10-year survival rate (%)	56% (47% to 68%)	33% (16% to 54%)					55% (95%CI 45% to 65%)	32% (95%CI 26% to 39%)		
Other survival rate (%)					Predicted 6-year 93.3%	Predicted 6-year 54.5%			7-year 58% (50% to 65%)	7-year 32% (22% to 41%)
Time at which group had survival advantage	After 4 years	Before 4 years					VS. chemo after approx 3 years VS IFN-α after approx 5 years	**HU/ BU** before 3 years **IFN-α** Before 5 years	After 5.5 years	Before 2.5 years

IFN-α= interferon alpha, BMT= bone marrow transplant, HU= hydroxyurea, BU= Busulphan, NA= not applicable, chemo=chemotherapy

4.4.4 Adverse effects

None of the included studies reported side-effects for the IFN-α treatment arms. Three of the five included studies did report complications arising from BMT (Table 20). Complications included graft versus host disease (up to 38%), death due to complications (up to 45%), infections (up to 33%).

Table 20 Adverse events reported with bone marrow transplantation

Study	**Italian Cooperative Study, 1999[79]**	**Ohnishi *et al.*, 2000[11]**	**Gaziev *et al.*, 2002[10]**
Complications	**BMT**	**BMT**	**BMT**
Death due to transplant related complications	43/120 (36%)	-	47/105 (45%)
Death due to GVHD	-	**Related donors** 1/15 (7%) **Unrelated donors** 3/8 (38%)	-
Death due to thrombocytopenic purpura	-	**Unrelated donors** 1/8 (13%)	-
Rejection or graft failure	-	-	0
GVHD* (grade II-IV)	-	-	38/100 (38%)
GVHD* (grade III-IV)	-	-	23/100 (23%)
Fungal infections	-	-	33/100 (33%)
Candida species infections	-	-	24/100 (24%)
Cytomegalovirus infection	-	-	13/100 (13%)
Relapse	15/120 (13%)	-	16/105 (15%)

*GVHD= graft versus host disease which is a complication of bone marrow transplantation where there is a reaction of donated bone marrow against a patient's own tissue. It can be fatal and is due to the donor's immune cells recognising the host cells as foreign.

4.4.5 Research in progress

The search strategy identified 2 studies comparing BMT and IFN-α that are currently in progress (See Appendix 10.8.6, page 127). It is reported that these trials have been halted because of poor recruitment subsequent to the advent of imatinib (personal communication, Professor J Apperley).

4.5 Indirect comparison imatinib versus hydroxyurea

Section 4.2.3 (page 43) demonstrated that imatinib was more effective than IFN-α+Ara-C in terms of surrogate outcomes (HR and CR) and progression free survival. Section 4.3.3 (page 51) demonstrated that IFN-α was superior to HU in terms of overall survival and CR. It is therefore likely that in a similar group of patients' imatinib will be more effective than HU for first line treatment of patients with chronic phase CML.

Table 21 shows that imatinib is associated with much higher rates of CR and HR than hydroxyurea. Survival with imatinib is slightly higher and withdrawal due to adverse events is similar compared to hydroxyurea. Such a comparison must be made with caution and assumes that patient groups are comparable which may not be the case.

We are unable to comment on the relative efficacy in subgroups of higher risk patients, older patients or those with co-morbidity, due to the lack of appropriate data for comparisons.

Table 21 Comparison of main results for hydroxyurea and imatinib

Study	Benelux, 1998[5]	Broustet, 1991[6]	Hehlmann, 1994[78]	The Italian Cooperative Study Group on CML, 1998[21]	Median from HU studies (range)	Imatinib (Novartis study 0106)[60]
Treatment	**HU**	**HU**	**HU/BU**	**HU**	**HU**	**IM**
Median survival	66 months	-	56.2 months	52 months	56.2	N/a
%1-year survival	97	-	96	96	96 (96-97)	98.0
% complete HR	42	-	-	39	41 (39-42)	94.6 (95%CI 92.3-96.3)
% partial HR	-	88	-	51	70 (51-88)	
% major HR	-	-	0	90	45 (0-90)	
% complete CR	0	0	0	1	0 (0-1)	67.8
% partial CR	2	31	1	1	2 (1-31)	14.8
% major CR	2	31	1	2	2 (1-31)	82.6 (95%CI 79.2-85.7%)
%Withdrawal due to side effects	4	4	-	1	4 (1-4)	2.0

IFN-α= interferon alpha, HU=hydroxyurea, BU=busulphan, IM= imatinib, HR= haematological response, CR= cytogenetic response

Hydroxyurea is generally considered to be well tolerated. Table 22 shows reported rates of adverse effects with hydroxyurea. This is compared to 41% of patients taking imatinib suffering a grade 3 or 4 event at some time (Table 14), but only 2% discontinuing treatment because of adverse effects. It is however possible that the severity of events differ and that reporting for imatinib has been more vigilant.

Table 22 Reported adverse events associated with hydroxyurea

Adverse effect	Benelux[5]	Broustet[6]	Hehlmann[7] [8]	The Italian Cooperative Study Group on CML[21]
	HU	HU	HU	HU
Fatigue, fever, pain, headache	2.1%	-	0.5%	-
Renal including vasculitis	1.1%	-	-	-
Drug eruption	1.1%	-	-	-
General intolerance	-	11.5%	-	-

4.6 Indirect comparison imatinib versus bone marrow transplant

When considering short-term follow-up, imatinib has better outcomes (progression free survival) than IFN-α+Ara-C (Section 4.2.3, page 43), whereas IFN-α has better survival than BMT (Section 4.3.3, page 51). By inference it therefore seems that imatinib is likely to be associated with better survival than BMT in approximately the first 4 years. It is not possible to comment on the longer-term relative survival of the two treatments due to the lack of longer-term imatinib data.

It is reasonable to assume that treatment with imatinib (Table 14, Table 15, Table 16) will be associated with less adverse events in the short term than BMT (Table 20). The spectrum of events is also likely to be very different. Once again caution needs to be made when making such comparisons, as populations may not be similar.

5 ECONOMIC ANALYSES RESULTS

5.1 Results of systematic review of existing economic literature

Only one published abstract of an economic evaluation of imatinib was identified, along with three published economic evaluations of IFN-α, and two published evaluations of BMT. We briefly describe and assess the abstract of Imatinib and also briefly evaluate economic studies of IFN-α and BMT in the treatment of CML. These IFN-α and BMT evaluations have been considered for comparative purposes, in order to assist judgements about the validity and robustness of the economic evaluations for imatinib.

The imatinib abstract outlines a Markov cost-utility analysis (see section 5.1.1 below for description of Markov models) of Imatinib compared to HU in chronic phase and combination chemotherapy or palliative care in the accelerated and blast phases.

Two published studies present decision analyses and Markov models comparing the cost-effectiveness of IFN-α to HU.[80] One study performed an economic analysis of IFN-α usage in CML using a Gompertz function to model survival.[81]

One BMT evaluation is a study of the costs and cost-effectiveness of unrelated donor transplantation for chronic phase CML and the other is a Markov model decision analysis comparing early, delayed and no transplantation for people with chronic phase CML.

It should be noted that across the identified economic studies there is likely to be wide variation in health systems which will affect costs and results. We have presented results as they are reported. Caution is necessary when applying results to another setting as they may not be transferable.

5.1.1 Markov models

A Markov model is a type of mathematical model containing a finite number of mutually exclusive and exhaustive health states, having periods of uniform length, and in which the probability of movement from one state to another depends on the current state.[82] The transition probabilities are applied to each "cycle" of the model, the cycle being of fixed duration, and are the probability of moving from one state to another.

Markov models allow for the synthesis of data on costs, effects, and health related quality of life, of alternative clinical strategies through the calculation of life expectancy, quality-adjusted life expectancy and lifetime costs, by tracking a simulated hypothetical cohort through the model.[83]

One of the main limitations of Markov models is the underlying assumption often referred to as 'zero memory'. Transition probabilities depend only on current health state and not on past health states.[84] Another limitation is the assumption that all people in a particular health state are identical. The assumptions are unlikely to be met in practice but it is difficult to determine the impact of this on overall results.[83]

5.1.2 Economic analysis of Imatinib (abstract only)

Warren, 2002[85]

The aim of this evaluation was to summarise the clinical evidence and perform an economic evaluation of Imatinib for chronic, accelerated and blast phases of CML. A Markov model was developed and showed the progression of a cohort of CML patients receiving imatinib or the comparative treatments (HU in chronic phase and combination chemotherapy or palliative care in accelerated and blast phases).

Clinical data on HR and CR and disease progression were obtained from three studies (references not provided). The abstract does not provide the utility values nor describe how they were obtained.

The incremental cost-effectiveness of imatinib over HU in chronic phase was £35,002 per QALY, of imatinib compared to combination chemotherapy or palliative care in accelerated phase was £21,826 per QALY and in blast phase £43,467 per QALY. The year of costs was not stated but the abstract was presented in 2002.

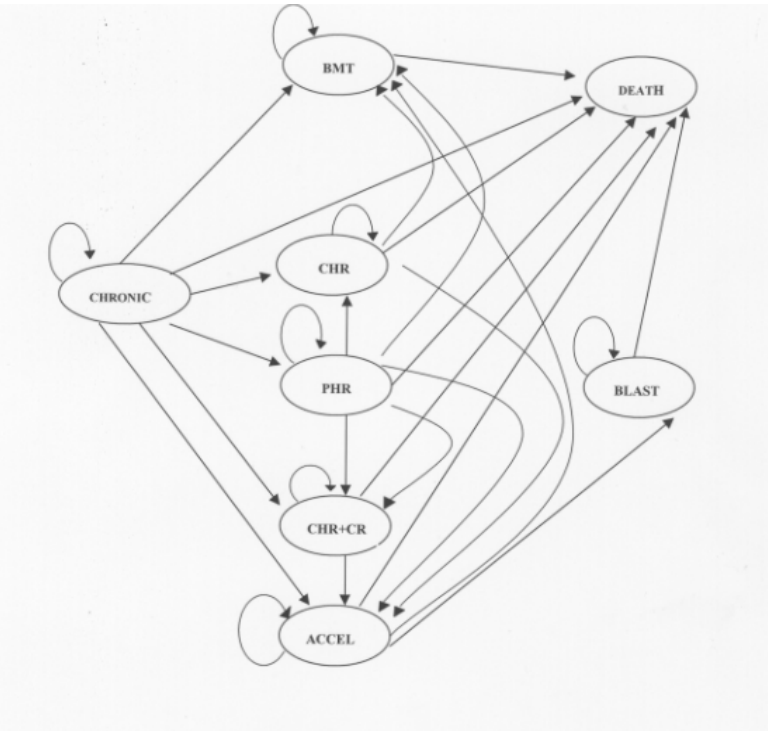
The abstract did not provide details of sensitivity analysis. The authors concluded, “there is strong evidence to suggest that Glivec is associated with high rates of response resulting in comparatively high long-term survival rates and an acceptable cost per QALY ratio”. Given the lack of long-term survival data this conclusion does not appear warranted.

5.1.3 Economic analysis of interferon alpha

Kattan RW, 1996[86]

The aim of this evaluation was to compare the cost-effectiveness of IFN-α and HU as first line therapy for patients with CML. A Markov model was developed containing 8 health states (haematological response (HR) + cytogenetic response (CR), complete haematological response without cytogenetic response (CHR), partial haematological response (PHR), chronic phase, accelerated phase, blast phase, BMT and death). In this model it is possible to progress to death from all other health states.

Figure 8 Influence diagram showing transitions between health states in Markov model used by Kattan[86]



Clinical data on survival, HR and CR were obtained from studies by Hehlmann,[78] The Italian Co-operative Study Group on CML,[87] Ozer[88] and Kantarjian.[89] Utilities were assessed by a clinical panel, and were 0.9 for patients receiving IFN-α therapy, 1.0 for patients receiving HU therapy and 0.5 for patients in blast or accelerated phases.

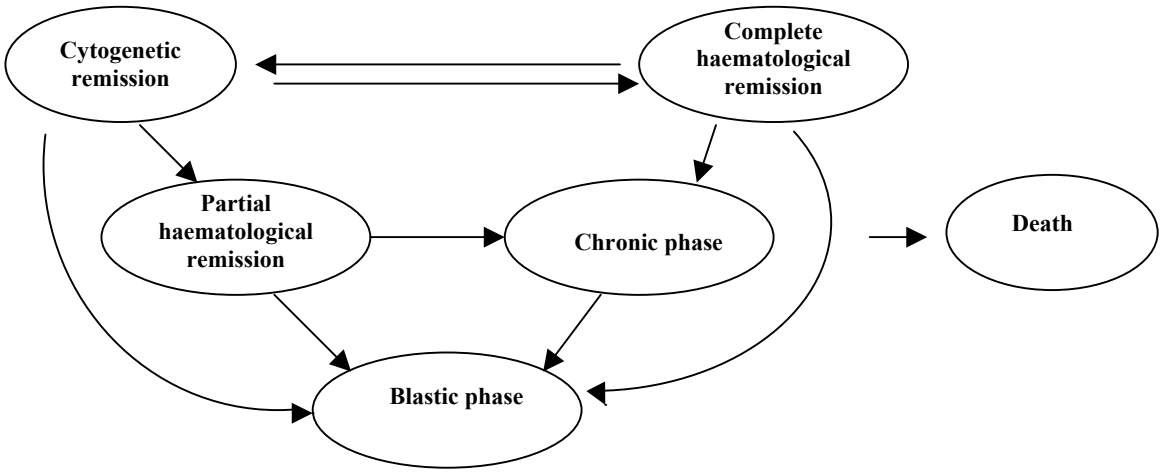
The incremental cost-effectiveness of IFN-α over HU was US$26,500 per life-year saved. When adjusted for quality of life the estimated cost-effectiveness ratio increased to US$34,800 per QALY. Year of costs was not stated but the paper was published in 1996.

The cost-effectiveness ratio of IFN-α was dependent on the age of the patient and the monthly cost of IFN-α, with the cost-effectiveness ratio being most favourable in younger patients. The authors concluded that compared with HU, IFN-α is, in most clinical scenarios, a cost-effective initial therapy for patients with chronic phase CML who can tolerate the drug.

Liberato 1997[80]

The purpose of this study was to evaluate the cost-effectiveness of IFN-α compared to conventional chemotherapy in patients with CML. A decision analysis was designed which incorporated a Markov model to estimate the cost-utility of IFN-α.

Figure 9 Influence diagram showing transition between health states in Markov model used by Liberato[80]



It is unclear from the study report whether patients can progress to death from all health states. Two scenarios were modelled:

1. Prolonged treatment for patients who achieved a haematological response
2. Prolonged treatment only for patients who achieved a cytological remission within 2 years.

Effectiveness data were taken from nine studies, including five RCTs. Interferon treatment increased quality-adjusted life expectancy by 15.5 months (scenario 1) and 12.5 months (scenario 2) relative to conventional chemotherapy. Utilities were estimated by 10 physicians and were 0.875 for patients receiving IFN-α therapy, 0.98 for patients on HU, 0.94 for patients receiving BU and 0.5 for patients in blast phase. The study reports an ICER of US$89,500 (scenario 1) and US$63,500 (scenario 2) per quality adjusted life-year gained. The year in which these costs were based is not stated but the paper was published in 1997.

The results were sensitive to the cost of IFN-α therapy and the probability of cytogenetic response. The authors conclude that IFN-α is substantially superior to conventional chemotherapy in terms of quality-adjusted survival, but at current doses the ICERs range from US$50,000 to US$100,000 per QALY gained.

Messori, 1998[81]

The aim of this evaluation was to assess the cost-effectiveness of IFN-α treatment for CML. The total area under the survival curve for each drug was calculated, using a Gompertz function to extend the observed one-year survival curve (the Gompertz function is frequently used to estimate survival curves.) No adjustment for the quality of life-years gained was included.

Four RCTs formed the basis of the effectiveness data. The incremental cost-effectiveness ratio (ICER) of IFN-α versus cytotoxic therapy ranged from US$93,000 to US$226,000 per discounted life-year gained (with the study published in 1998 – no cost year is given).

Conclusions were sensitive to the dose of IFN-α used. When adding in a non-randomised trial with particularly favourable results for IFN-α the cost-effectiveness ratio ranged from US$56,022 for a dose of 10MU per patient per week to $204,680 for a IFN-α dose of 60MU per patient per week.

The authors of this evaluation conclude that a long-term treatment with IFN-α without careful selection of patients may not be cost-effective.

Table 23 summarises the results of the three cost-effectiveness studies comparing IFN-α to chemotherapy for CML.

Table 23 Summary of cost-effectiveness studies comparing IFN-α and chemotherapy.

Study	ICER
Kattan *et al*., 1996[90]	US$34,800 per QALY gained
Liberato *et al*., 1997[80]	US$89,500 and US$63,500 per QALY gained
Messori *et al*., 1998[91]	US$93,000 to US$226,000 per life-year gained

There is a wide range of estimates for the cost-effectiveness of IFN-α for CML. There are several reasons for this variation. Firstly, there are obvious differences in methodology with the Liberato[80] and Kattan[86] studies using Markov models to calculate cost per QALY, and the Messori study[81] using a Gompertz model without quality adjustment of life-years gained. Quality adjustment in the latter is likely to further increase the incremental cost-effectiveness ratio.

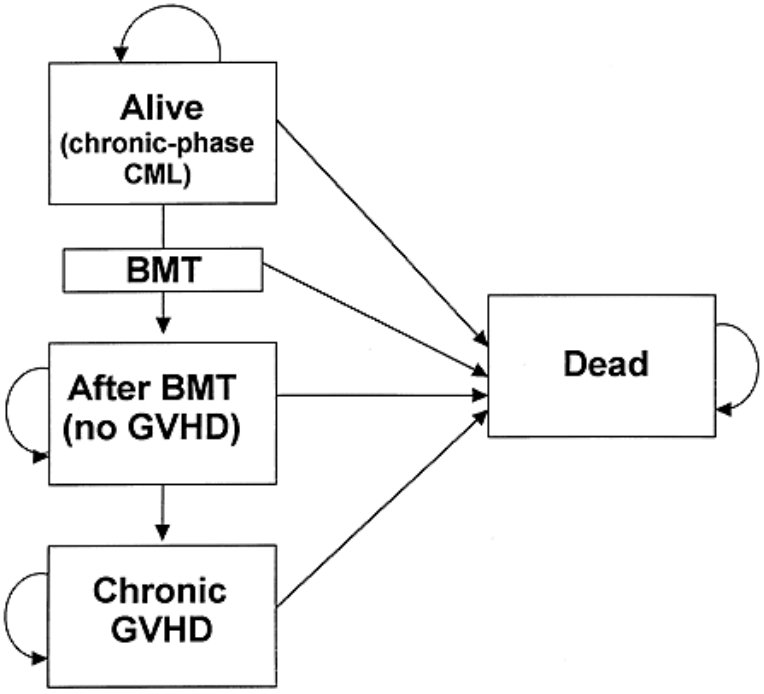
The estimates from the Liberato study[80] are similar to the lower estimates of the Messori Study.[81] The combination of higher survival values and lower costs of IFN-α therapy account for the Kattan study significantly lower ICERs than Liberato[80] or Messori.[81] Kattan and colleagues[86] also used slightly higher values of estimated survival gains from IFN-α than the other two studies[81,80]. Kattan and colleagues[86] also used lower estimates of cost per patient of IFN-α therapy than the other two studies, as IFN-α therapy is more expensive in Italy than in the United States. Kattan and colleagues[86] did not include costs such as drug administration, laboratory processing and physician time in contrast to the Messori study[81] .

5.1.4 Economic analysis of bone marrow transplant

Lee *et al.*, 1997[92]

The aim of this evaluation was to compare early, delayed and no transplantation for patients with chronic phase CML. A Markov model was constructed that compared different strategies and considers age, quality of life, risk aversion and the competing risks for CML progression and transplant toxicity. The model contains five states illustrated in Figure 10.

Figure 10 Influence diagram showing transitions between health states in Lee and colleagues[92]



The life expectancy of patients not receiving transplants was obtained from published studies by Ohnishi,[93] Allan,[94] The Italian Cooperative Study Group on CML,[95] Sokal,[96] Hehlmann,[97] Sonnenberg[98] and Hehlmann.[7] Survival curves were extrapolated by using a function fitted to the clinical data. Outcomes for those who underwent unrelated BMT were obtained from two registries, and inputs for graft versus host disease were obtained from a published study by McGlave[99] Utilities were derived using the standard gamble method with 12 physicians and were 0.979 for life without chronic GVHD after transplantation and 0.9 for life with chronic GVHD after transplantation.

The results of the evaluation showed that for newly diagnosed patients with CML transplantation within the first year provides the greatest quality adjusted expected survival, although this benefit decreases with increasing patient age. Then authors give an example of a 35-year-old patient with an intermediate prognostic score. Transplantation within the first year results in 5.3 more discounted QALYs than no transplantation. Results were shown to be reasonably robust in sensitivity analysis.

Lee *et al.*, 1998[100]

The aim of this study was to assess the costs and cost-effectiveness of unrelated donor BMT for chronic phase CML. This study builds on the Markov model described above[92] by incorporating extensive cost data. It specifically compares BMT within the first year after diagnosis and IFN-α or HU.

Effectiveness and utilities were used as described above.[92] Cost data was obtained from retrospective analysis of two cohorts of patients undergoing BMT at separate hospitals, the Red Book (USA national formulary) and hospital accounting systems. The following cost data were obtained for people undergoing BMT: donor identification, pretransplant testing, marrow collection, inpatient and outpatient care costs and outpatient medication costs. The

following costs were obtained for non-transplant management of CML: medication costs, outpatient visits, phlebotomy, blood tests, inpatient costs for induction chemotherapy and hospitalisation for blast crisis.

The ICER of transplantation within 1-year of diagnosis versus non-transplantation in the base case of a 35 year old patient was US$51,800 per QALY gained, with sensitivity analysis ratios ranging from US$50,000 to US$100,000. All costs were adjusted to 1996 dollars.

5.2 Cost effectiveness and cost utility of imatinib- independent economic model

5.2.1 Key model parameters

This section describes and tabulates the key inputs used as base case estimates in the independent economic model. Table 24 shows the costs that are used in the model (see section 3.2.2, page 32 for a description of methods).

Table 24 Description of costs and amount per month used in the economic model

Drug/test	Health state	Dose/ Number per cycle	Cost per month	Source
Imatinib	Chronic and CR	400mg/ day	£1580.72	BNF 44, dose from Novartis study 0106, 2002[60]
Imatinib	Accelerated and loss of CR	600mg/ day	£2371.08	BNF 44
Interferon alpha	Chronic and CR	5MU/ day	£1109.90	BNF 44, dose from Novartis study 0106, 2002[60]
Interferon alpha	Accelerated and loss of CR	5MU/ day	£1109.90	BNF 44
Hydroxyurea	Chronic, Accelerated	2g/ day	£14.56	BNF 44, dose from Novartis study 0106, 2002[60]
Mercaptopurine	Blast	150mg/ day	£67.05	BNF 44
Outpatient visit	Chronic Accelerated Blast	1 (SD 0.33) 3 (SD 1) 6 (SD 2)	£114.00 (half initial and half follow up visits)	Clinical estimate, cost from SUHT database 2001/02
Bone marrow test	Chronic Accelerated Blast	0.5 (SD 017) 0.5 (SD 0.17) 1 (SD 0.33)	£271.00	Clinical estimate, cost from SUHT database 2002/03
Blood transfusion	Chronic Accelerated Blast	0.25 (SD 0.08) 0 9 (SD 3)	£3243 (composed of 20 units of full blood, 10 units of platelets and 2 hours nursing time grade D/E)	Clinical estimate, cost from Novartis, study 0106, 2002[60]
Radiology test	Chronic Accelerated Blast	0 0 9 (SD 3)	£54 (1 X-ray and 1 CT scan)	Clinical estimate, cost from SUHT database 2002/03
Inpatient visit	Chronic Accelerated Blast	0 0 3 (SD 1)	£209 per day (each stay is 3 days)	Clinical estimate, cost from SUHT database 2001/02

SD= standard deviation used to randomly sample from a normal distribution for probabilistic sensitivity analysis

The number of outpatient visits, bone marrow tests, blood transfusions, radiology tests and inpatient visits were modelled in the probabilistic sensitivity analysis by assuming a standard deviation of one third the number of visits/tests and randomly sampling from a normal distribution.

Table 25 shows the utilities associated with the various health states as used in the independent economic model (see section 3.2.2, page 33 for a description of methods).

Table 25 Utility values associated with health states used in the independent economic model

Health states	Utility values (SD)	Source	Distribution used in probabilistic sensitivity analysis
Chronic phase- Imatinib treatment	0.8539 (0.1925)	Novartis study 0106, 2002 [60]	Beta
Chronic phase- Imatinib treatment after loss of CR	0.8539 (0.1925)	Novartis study 0106, 2002 [60]	Beta
Chronic phase- Interferon alpha treatment	0.7104 (0.2658)	Novartis study 0106, 2002 [60]	Beta
Chronic phase- Interferon alpha treatment after loss of CR	0.7104 (0.2658)	Novartis study 0106, 2002 [60]	Beta
Chronic phase- Hydroxyurea treatment	0.9 (0.2*)	Kattan, 1996[86]	Beta
Cytogenetic response- Imatinib treatment	0.8539 (0.1925)	Novartis study 0106, 2002 [8]	Beta
Cytogenetic response- Interferon alpha treatment	0.7104 (0.2658)	Novartis study 0106, 2002 [60]	Beta
Accelerated phase- Imatinib treatment	0.729 (0.204)	Novartis study 0106, 2002 [60]	Beta
Accelerated phase- Interferon alpha treatment	0.729 (0.204)	Novartis study 0106, 2002 [60]	Beta
Accelerated phase- Hydroxyurea treatment	0.729 (0.204)	Novartis study 0106, 2002 [60]	Beta
Blast phase - Mercaptopurine	0.524 (0.424)	Novartis study 0106, 2002 [60]	Beta

* estimated

Table 26 and Table 27 show the relative risks applied to the independent economic model for survival/ progression, response and risk score (see section 3.2.2, page 33 for a description of methods).

Table 26 Relative risks of imatinib and hydroxyurea compared to interferon alpha used in the economic model for survival, progression and response.

Relative Risk	Interferon alpha*	Imatinib (SE)	Source of imatinib estimate	Hydroxyurea (SE)	Source of hydroxyurea estimate	Distribution used in probabilistic sensitivity analysis
Progression	1	0.8347 (0.103)	Modelled from 18 month data Novartis study 0106,[60] using an exponential distribution	1.26 (0.103)	Benelux *et al.*, 1998[5]	Log normal
Mortality	1	0.5872 (0.25)	Modelled from 18 month data Novartis Study 0106,[60] using a Weibull distribution	1.19 (0.106)	Benelux *et al.*, 1998[5]	Log normal
Cytogenetic response	1	3.41 (0.130)	Based on 12 month data from Novartis study 0106, 2002[60]	0	Not applicable	Log normal

*hydroxyurea and imatinib are modelled relative to interferon alpha, therefore the RRs for interferon alpha are equal to one

The risk score relative risks were calculated using the Italian Study Group's Sokal data.[21]

Table 27 Relative risks for all treatments according to risk score

Risk score	All treatments	Source of estimate	Distribution used in probabilistic sensitivity analysis
Low versus intermediate	1.197	Hazard ratio calculated from the Italian Sokal study[28]	Log normal
Low versus high	1.280	Hazard ratio calculated from the Italian Sokal study[28]	Log normal

In addition the following assumptions were included in the economic model (see section 3.2.2, page 29 for a description of methods):

- Overall death rate was modelled from the mortality curve of the Italian trial[21]. It was assumed that 60% of those in blast crisis were dead in 6 months.
- Complete CR is only possible from the chronic phases within the model
- It is assumed that 30% of all progression from chronic phase is to accelerated phase and 70% to blast phase (based on data from Novartis Study 0106, 2002[60]
- Transitions from Chronic to CR are only permitted in the first 5 years of the model
- The number of outpatient visits, bone marrow tests, radiology tests, inpatient visits and blood transfusions are the same for a given phase regardless of assigned treatment
- Admissions to hospital in blast phase are assumed to be for 3 days
- A cytogenetic response is not possible for those treated with HU

Table 28 outlines the transitions between health states used in the independent economic model (see section 3.2.2, page 29 for a description of methods and see Figure 1 and Figure 2 for a flow chart).

Table 28 Transition values and sources used in the independent economic model

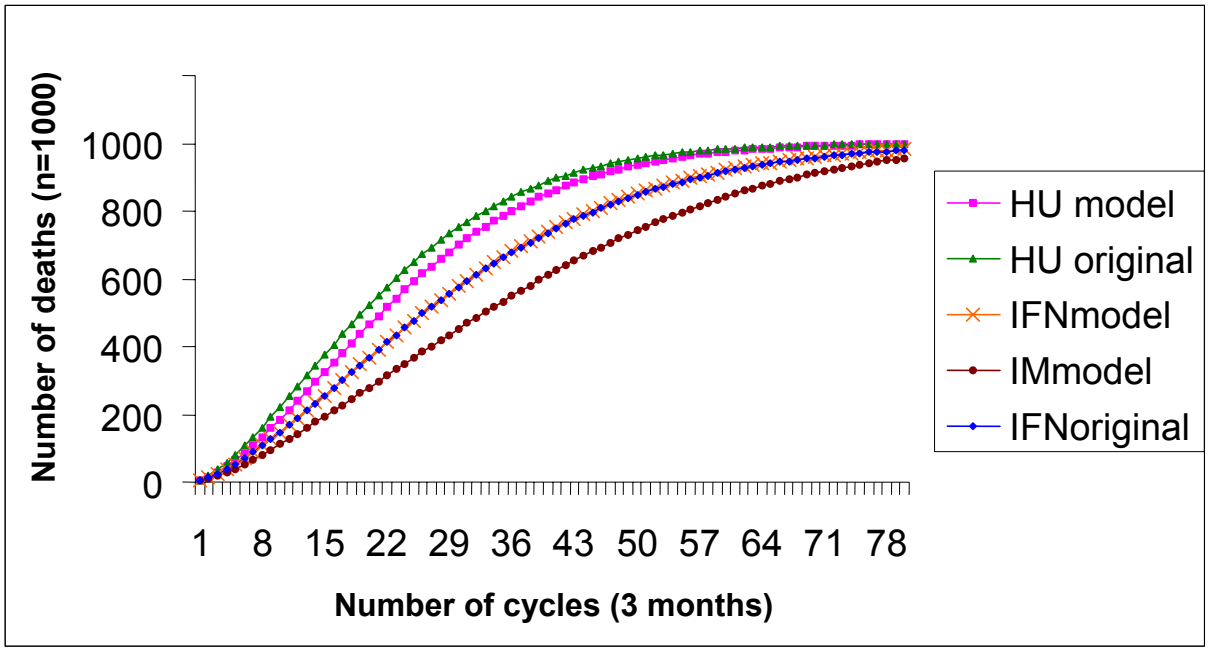
Transition	Value	Source
First line treatment		
Chronic to accelerated	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Chronic to blast	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Chronic to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Accelerated to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Blast to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
CR to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Chronic to CR	Median time to response 18 months (probability 0.0085 per cycle)	Italian Cooperative Study Group, 1998[21]
Accelerated to blast	Median time in accelerated phase 18 months (probability 0.109 per cycle)	Kantarjian, 1992[89]
CR to chronic 2*	Time to loss of response curve (cycle dependent)	Bonifazi, 2001[25]
2nd line treatment with IFN-α for those who failed imatinib		
Chronic 2* to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Chronic2* to accelerated	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Chronic2* to blast	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998[21]
2nd line treatment with IM for those who failed IFN-α		
Chronic2* to dead	Survival curve (cycle dependent)	
Chronic2* to accelerated	% progression curve (cycle dependent)	Kantarjian, 2002[59] (for 1st 5 cycles) Italian Cooperative Study Group, 1998[21] (for cycles 6 onwards)
Chronic2* to blast	% progression curve (cycle dependent)	Kantarjian, 2002[59] (for 1st 5 cycles) Italian Cooperative Study Group, 1998[21] (for cycles 6 onwards)
Chronic2* to CR	Time to response curve (cycle dependent for first 5 cycles)	Kantarjian, 2002[59] (1st 5 cycles, then the rate from cycle 5 for cycles 6-20, then no response)

*chronic2 is a state for those who lost their CR but have not progressed

5.2.2 Validation of curves

In order to validate the survival and progression data used in the model, model-derived data were plotted on the same graph as original data. Comparisons showed similar curves for progression and survival (Italian Cooperative Study Group, 1998) [21], as well as time to loss of cytogenetic response (Bonifazi, 2001).[25] A more detailed description and figures are shown in Appendix 10.9 (page 128).

Figure 11 Model output data compared to original data from the Italian Cooperative Study



5.2.3 Results of economic model

Discounted and undiscounted cost-utility estimates (ICERs) are shown in Table 29 and Table 30 respectively.

Table 29 Discounted cost per QALY of interferon alpha and hydroxyurea compared to imatinib

Drug		Cost per person	QALYs per person
HU	£	38,322	4.99
Imatinib	£	215,684	7.03
IFN-α	£	163,581	5.04
ICERs:			
Imatinib versus HU	£	86,934	per QALY
IFN-α versus HU	£	2,505,364	per QALY
Imatinib versus IFN-α	£	26,180	per QALY

Table 30 Undiscounted cost per QALY of interferon alpha and hydroxyurea compared to imatinib

Drug		Cost per person	QALYs per person
HU	£	46,591	5.01
Imatinib	£	235,403	7.25
IFN-α	£	167,052	5.10
ICERs:			
Imatinib versus HU	£	84,100	per QALY
IFN-α versus HU	£	1,293,948	per QALY
Imatinib versus IFN-α	£	31,761	per QALY

Sub-group cost-utility analysis was also performed and the following tables show the cost per QALY of interferon alpha and hydroxyurea compared to imatinib for low risk patients and high-risk patients (Table 31 and Table 32, and see Table 27 for values used).

Table 31 Discounted cost per QALY of interferon alpha and hydroxyurea compared to imatinib for intermediate risk patients

Drug		Cost per person	QALYs per person
HU	£	31,105	4.52
Imatinib	£	188,525	6.30
IFN-α	£	135,158	4.50
ICERs:			
Imatinib versus HU	£	88,459	per QALY
IFN-α versus HU	-£	*4,507,569*	per QALY
Imatinib versus IFN-α	£	29,605	per QALY

Table 32 Discounted cost per QALY of interferon alpha and hydroxyurea compared to imatinib for high-risk patients

Drug		Cost per person	QALYs per person
HU	£	28,777	4.35
Imatinib	£	179,417	6.04
IFN-α	£	125,982	4.31
ICERs:			
Imatinib versus HU	£	89,045	per QALY
IFN-α versus HU	-£	*2,120,182*	per QALY
Imatinib versus IFN-α	£	30,753	per QALY

In all scenarios presented in this section imatinib is more costly than IFN-α and HU but also produces more QALYs. The ICER of imatinib compared to IFN-α ranged from £26,180 to £31,761. On the other hand IFN-α does not appear to be cost-effective compared to HU and is associated with more cost and similar QALYs. This is because the adverse effects have a marked impact on the utility valuation of IFN-α +Ara-C. For intermediate and high risk patients, interferon is dominated by HU (less QALYS and more expensive)

5.2.4 Sensitivity analysis

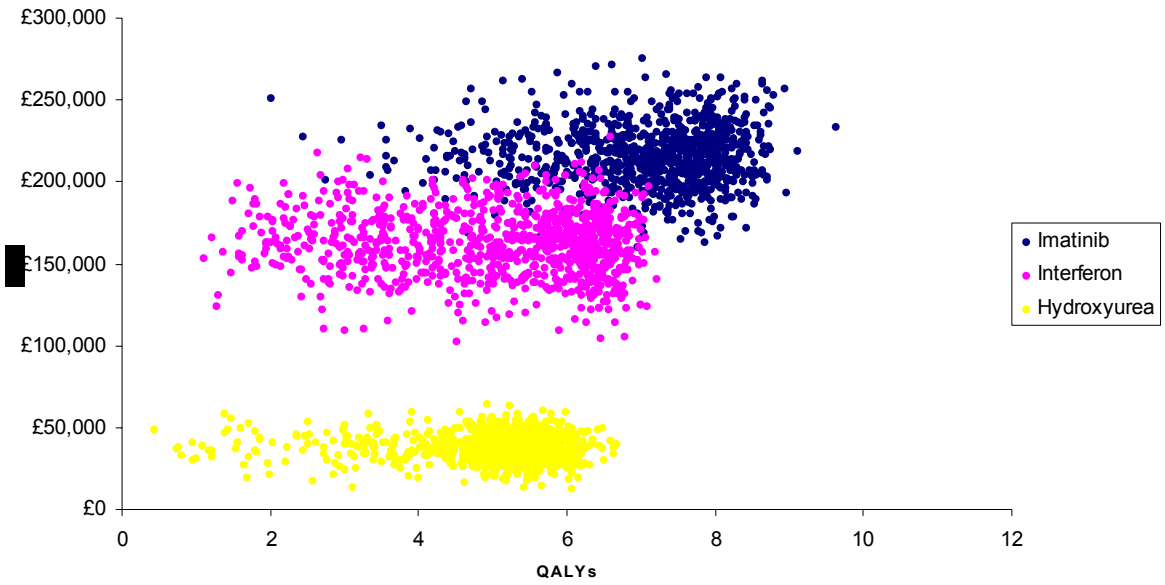
A probabilistic analysis was undertaken to explore the effects of uncertainty in model parameters on outputs. Results are presented in Table 33 , showing the average results obtained from 1000 simulations. (For a description of methods see section 3.2.2, page 34).

Table 33 Discounted cost per QALY of interferon alpha and hydroxyurea compared to imatinib from probabilistic analysis

Drug	Cost per person	QALYs per person
HU	£ 37,950	4.98
Imatinib	£ 215,927	7.03
IFN-α	£ 162,591	5.06
ICERs:		
Imatinib versus HU	£ 86,901	per QALY
IFN-α versus HU	£ ,620,474	per QALY
Imatinib versus IFN-α	£ 27,059	per QALY

The results of each of the simulations is plotted on a cost-effectiveness plane in Figure 12. Costs and QALYs are presented for each of the three treatments (each treatment represented by a different marker).

Figure 12 Cost effectiveness plane for the independent probabilistic economic analysis



The probabilistic analysis also generates a cost-effectiveness acceptability curve. This is a way of relating uncertainty in cost-effectiveness to the decision-makers maximum willingness to pay for an additional QALY gained (Figure 14 and Figure 15). The probability that a treatment is cost-effective at a particular maximum willingness to pay value is plotted. The

points are joined to form a curve. The ICER of two therapies is represented by the value at which the appropriate two lines cross. Imatinib and IFN-α cross at around £27,000, and imatinib and HU at about £86,000. It may be considered that HU is a less appropriate comparator than IFN-α for treatment in chronic phase CML as HU is less effective than IFN-α. It is used in those patients who cannot tolerate IFN-α treatment, or occasionally as first line treatment for other reasons such as frailty.

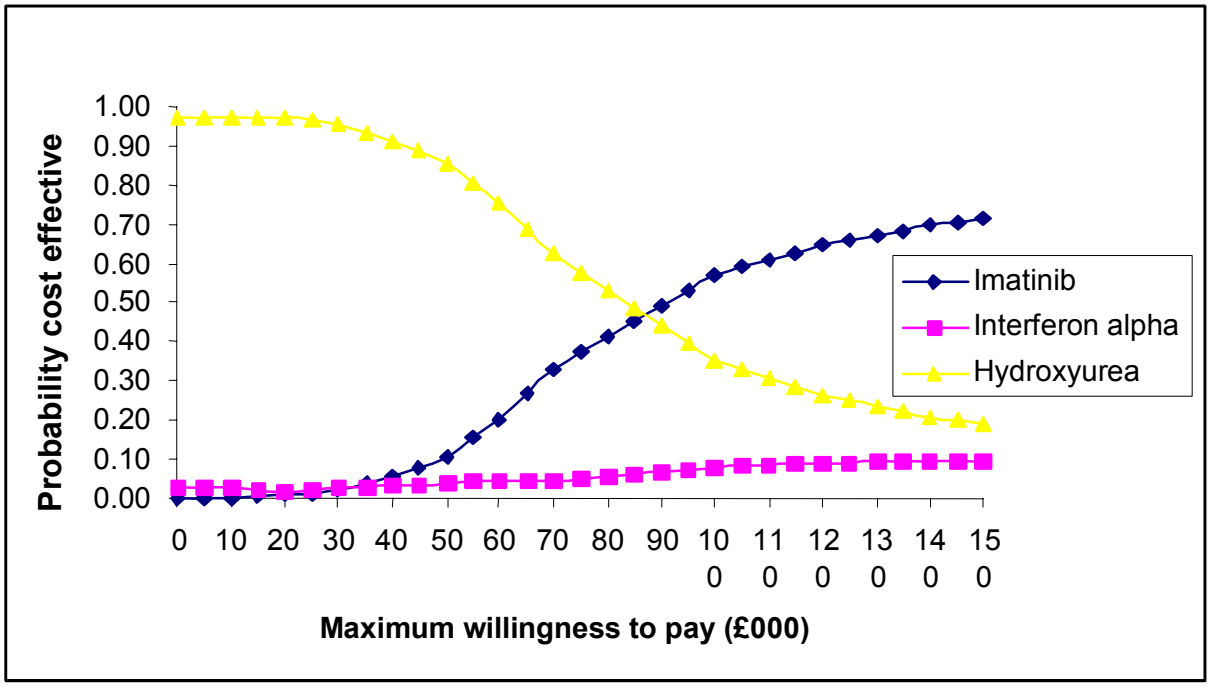
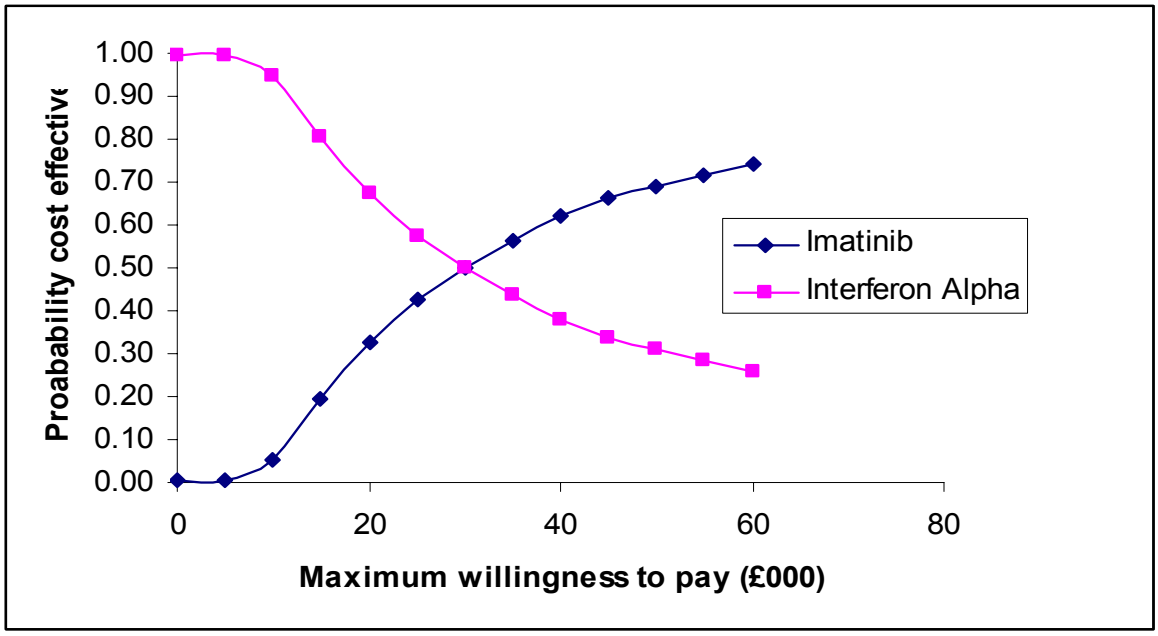


Figure 13: Cost effectiveness acceptability curve for IFN-α, imatinib and hydroxyurea

Figure 14: Cost effectiveness acceptability curve for IFN-α and imatinib



It can be seen that with three comparisons, HU has the greatest probability of being cost-effective up to a value of £95,000. If however, only imatinib and IFN-α are considered, imatinib becomes more cost-effective above £31,000.

In addition, a number of one-way sensitivity analyses were performed in order to determine the parameters to which results were most sensitive. A full description of the assumptions varied, the values used and justifications made are presented in Table 34 (methods are described in section 3.2.2, page 34).

Table 34 Sensitivity analysis values and sources

Assumptions	Value	Source
General		
Benelux survival curves	Survival curve (cycle dependent)	Benelux *et al.*, 1998[5]
Benelux progression curves	Survival curve (cycle dependent)	Benelux *et al.*, 1998[5]
Benelux survival and progression curves	Survival curve (cycle dependent)	Benelux *et al.*, 1998[5]
2nd line HU for all treatments		Arbitrary
Imatinib arm- 2nd line treatment with imatinib 600mg (chronic phase) and 800mg (accelerated phase)	Cost £2372/ month and £3161/ month	Arbitrary
Imatinib arm- 2nd line treatment with imatinib 400mg and IFN-α 3MU	Cost £1581/month and £395/ month	Study by O'Dwyer *et al.*, 2002[37]
Imatinib- 2nd line treatment with imatinib 600mg and IFN-α 5MU	Cost £2372/ month and £666	Study by O'Dwyer *et al.*, 2002[37]
Pegylated IFN-α instead of standard IFN-α	Cost £1104/ month	Studies by Trabacchi *et al.*, 2002[39] and O'Brien *et al.*, 2002[38]

Progression to blast and accelerated phases	30% and 60% of total progression	Clinician estimate from Novartis study 0106, 2002[60]
IFN-α chronic2- transitions same as 1st line IFN-α	Progression and survival curves (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Imatinib chronic2- transitions same as 1st line IFN-α	Progression and survival curves (cycle dependent)	Italian Cooperative Study Group, 1998[21]
Transitions from chronic to CR permitted	Only in first 3 years of model	Arbitrary
Transitions from chronic to CR permitted	Only in first 10 years of model	Arbitrary
Chronic to CR- median time to response	6 months	Arbitrary
Chronic to CR- median time to response	12 months	Arbitrary
Chronic to CR- median time to response	24 months	Arbitrary
Costs and QALYs discounted	6%	Arbitrary
Costs and QALYs discounted	0%	Arbitrary
Costs		
IM dose	600mg chronic 800mg accelerated	Arbitrary
IFN-α dose	3MU	Arbitrary
IFN-α dose	7MU	Arbitrary
OP visits- chronic -accelerated -blast	2 & 0.5 6 & 1.5 12 & 3	Double and half clinician estimate
BM tests- chronic -accelerated -blast	1 & 0.25 1 & 0.25 2 & 0.5	Double and half clinician estimate
Transfusion- chronic -accelerated -blast	0.5 & 0.125 0.25 18 & 4.5	Double and half clinician estimate
Transfusion (IM only)- accelerated	3, 6 & 9	Arbitrary
Radiology- chronic -accelerated -blast	0.5 0.5 24 & 6	Double and half clinician estimate
Inpatient visits- chronic -accelerated -blast	0.5 0.5 6 & 1.5	Double and half clinician estimate
Utilities		
Kattan estimates	Chronic IFN-α 0.9 Chronic HU 1.0 Accelerated 0.5 Blast 0.5	Kattan, 1996[86]
Novartis clinician estimates	Chronic IM 0.91 CR IM 0.91 Accelerated 0.01 Blast –0.09 HU 0.90 IFN-α 0.832	Novartis study 0106, 2002[60]
Novartis from study 0106	Accelerated 0.5952 Blast 0.5952 HU 0.8445	Novartis study 0106, 2002[60]
Relative risks for survival and progression		
Imatinib- progression -mortality -cytogenetic response	0.6, 0.7, 0.9 & 1.0 0.4, 0.5, 0.7, 0.8, 0.9, 1.0 1, 1.5, 2, 2.5, 3, 4, 4.5	Arbitrary
IFN-α- progression -mortality -cytogenetic response	0.8, 0.9, 1.1, 1.2 0.8, 0.9, 1.1, 1.2 0.8, 0.9, 1.1, 1.2	Arbitrary
Hydroxyurea- progression -mortality -cytogenetic response	1, 1.5, 2, 2.5 1, 1.5, 2, 2.5 0.25, 0.5, 1	Arbitrary

The estimate of cost-utility for imatinib compared to IFN-α is most sensitive to the dose of interferon, the type of second line treatment, chronic phase utilities and the relative risk of CR.

In general, the estimates were insensitive to the changes made. Sensitivity analysis results are shown for general assumptions, costs, utilities and relative risks of progression and survival in Appendix 10.10 (page 130). A summary of the sensitivity analyses resulting in ICERs above £30,000 and below £20,000 are shown in Figure 15 and Figure 16 respectively.

Figure 15: Summary of sensitivity analyses (imatinib versus interferon-alpha) resulting in ICERs above £30,000

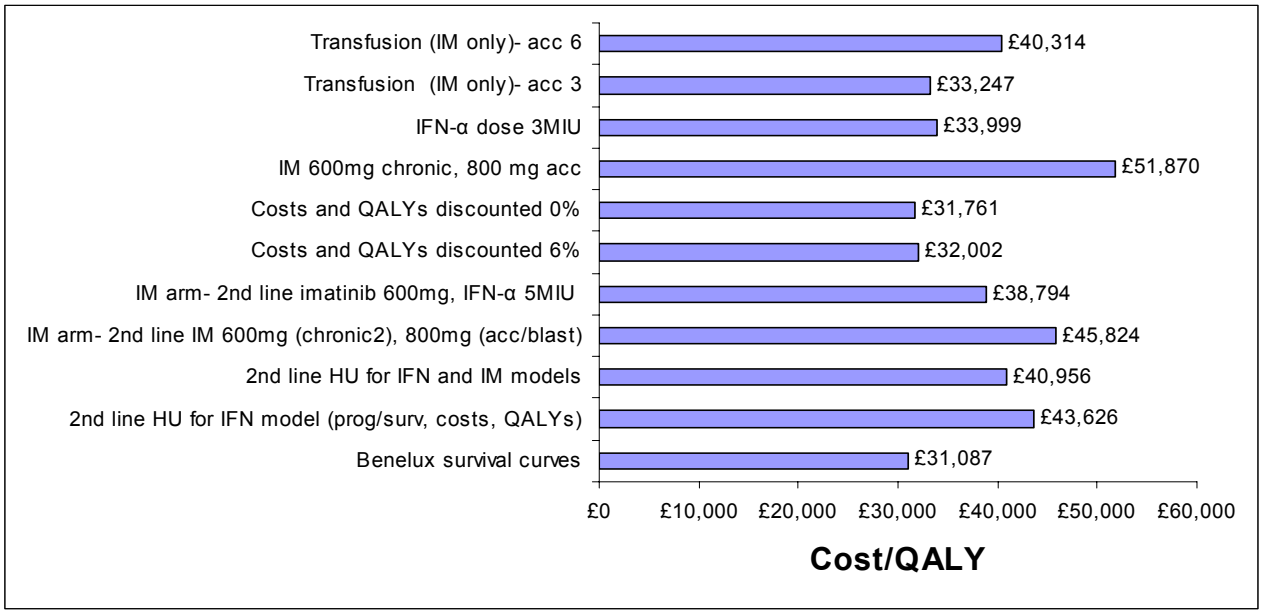
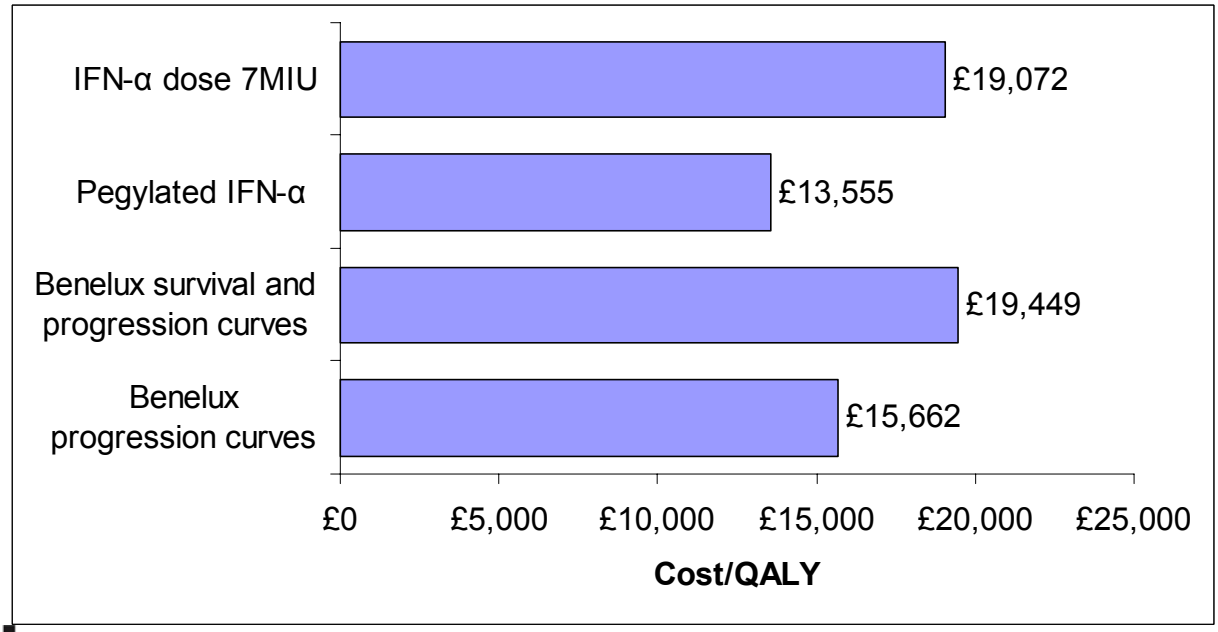


Figure 16: Summary of sensitivity analyses (imatinib versus interferon alpha) resulting in ICERs below £20,000



The comparisons between imatinib and HU were moderately sensitive to changes in the relative risk (survival and progression) of HU compared to IFN-α. If this relative risk is increased to 1.5, the ICER for imatinib/HU drops to £67,075. The model is not sensitive to the utility of HU and imatinib in chronic phase, with minimal change in the ICER (to £78,196). The comparison between IFN-α. and HU, is very sensitive to the assumptions about relative rsik fo survival and progression. The ICER drops to £190,303 when the relative risk is increased to 1.5. Given the uncertainty around this value, it would be unwise to draw any firm conclusions about the ICER for IFN-α and HU.

The range of ICERs when considering all one-way sensitivity analyses for imatinib compared to IFN-α was £13,555 to £51,870 (see Appendix 10.10, page 130). There were no reasonable assumptions under which dominance shifted to IFN-α. The maximum estimate was obtained when assuming that the dose of imatinib would be increased to 600mg in chronic and accelerated phases and 800mg in blast phase. The minimum estimate was obtained when substituting survival and progression curves from the Benelux study.[5]

The ICER for imatinib compared to IFN-α falls within the range considered by many decsion makers as cost effective. This is due to a combination of markedly better utility values in the chronic phase and improved survival. If IFN-α is assigned equivalent utility values to imatinib, then the ICER is £42,556. If survival, progression and cytogenetic response of imatinib are identical to IFN-α, the ICER is £48,463. If the utility values for IFN-α are 0.75 or lower then the ICER remains under £30,000.

We have not modelled the cost of adverse effects. This is likely to favour IFN-α in the analysis as adverse effects are more common and severe with IFN-α, and hence would incur additional costs for no additional benefit. The utility values used were derived from patients, which is not strictly appropriate for a societal analysis. However, sensitivity analysis using clinician derived estimates (no public estimates were available) does not materially alter the conclusions.

5.3 Novartis economic model and comparisons with independent model

5.3.1 Novartis economic model

The purpose of this economic evaluation was to compare the cost-effectiveness of imatinib with IFN-α+Ara-C for the treatment of newly diagnosed patients with CML in whom BMT was not considered a therapeutic option. The model used a Markov structure (see section 5.1.1, page 58 for a description of methods) containing the following health states: chronic phase, complete HR, partial HR and complete CR, accelerated phase and blast crisis death. In this model it is only possible to die from CML from the blast state. From other states, deaths from non-CML causes are permitted.

The model crosses patients from imatinib to IFN-α+Ara-C and vice versa when they progress or lose a response. Third line treatment for all patients is HU. The model runs for 30 years.

The cost-effectiveness analysis is based on data from Novartis study 0106.[60] Two different methods were used to estimate survival:

CR method: Modelling the relationship between CR and survival based on the IFN-α literature and then applying this to the response rates seen in study 106. After 2 years survival is based on whether patients had a CR (during the first 2 years), independently of treatment (data taken from study by Bonifazi[25]).

PFS method: The imatinib group uses progression free survival (PFS) data from the Novartis study 0106[60] for the first 12 months, and then assumes the progression free survival of IFN-α+Ara-C for subsequent years (The Italian Cooperative Study Group, 1998[21]).

Unit costs were drawn from NHS sources. The following costs were included: drug treatment, palliative care (in hospital and at home), outpatient visits, bone marrow tests, blood transfusions, radiology tests and nurse visits. Costs were discounted at 6%. Quality of life data (EQ-5D) were obtained from trial 106 and provide utility estimates. QALYS were discounted at 1.5%.

The summary of results is presented in Table 35.

Table 35 Summary of results from Industry economic model

	IFN-α+Ara-C	Imatinib (survival modelled using method 1)	Imatinib (survival modelled using method 2)
Total cost (discounted)	£5,987,634	£14,950,238	£11,739,633
Total QALYs (discounted)	466	941	680
Incremental cost	-	£8,962,604	£5,751,999
Incremental QALYS	-	475	214
ICER	**-**	**£18,865**	**£26,850**

Sensitivity analysis varied the dose of IFN-α, the cost of hospitalisation, the cost and QALY discount rates. The model was most sensitive to the cost of IFN-α and the discount rate.

5.3.2 Quality assessment of Novartis model

Comments on the quality of the industry model, using combined criteria from the Drummond[83] and Sculpher[101] economic checklists are detailed in Appendix 10.11 (page 134).

5.3.3 Detailed comparisons between Novartis model and independent economic model

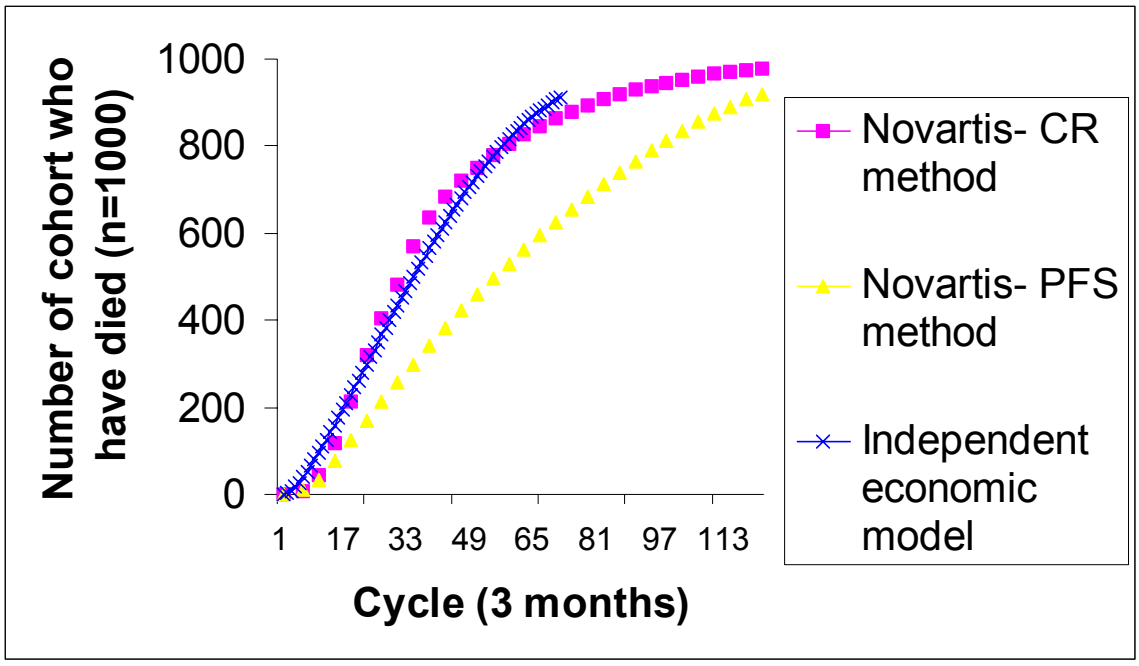
Table 36 summarises the ICERs produced by the Novartis models compared to the independent economic model.

Table 36 Comparison between of ICERs between independent economic model and Novartis' two models[60]

	Independent economic model	Novartis, 2002 (based on cytogenetic response approach)[60]	Novartis, 2002 (based on progression free survival approach)[60]
ICER imatinib versus IFN-α	£26,180	£18,865	£26,850

Figure 17 shows survival in the Novartis model compared to the independent economic model. The figure shows how many people have died at each time point, starting with a cohort of 1000 people. It can be seen that the Novartis CR approach and the independent model are reasonably similar with the independent model giving a higher death rate in the first couple of years and after approximately 12 years. The Novartis PFS approach gives a lower death rate than the other two techniques.

Figure 17: Survival from independent model compared to Novartis's two models



At the end of 20 years, a higher proportion of the Novartis cohort (7%) remain in CCR, compared to the independent model (2%). Somewhat perversely, it appears that prolonged survival is associated with a higher ICER, presumably because costs continue to accrue at a greater rate than benefits.

The independent model results in an ICER for imatinib and IFN-α that is similar to the Novartis PFS approach (despite survival being more similar to the CR approach). One of the main differences between the three models is the modelling of survival and progression. The Novartis models assume IFN-α+Ara-C survival rates for imatinib after 12 months. The independent economic model applies a continuing relative risk of benefit (for the length of the chronic phase) for imatinib. There is no long-term empirical data to support or refute either technique. If we are to change the independent economic model so that it too assumes IFN-α survival rates after 12 months the resulting ICER moves up to £38,411 for imatinib verus IFN-α (See Table 37).

Table 37 Results for the independent model when assuming IFN-α survival rates for the imatinib cohort after 12 months.

Drug		Cost per person	QALYs per person
HU	£	38,317	4.99
Imatinib	£	204,680	6.11
IFN-α	£	163,564	5.04
ICERs:			
Imatinib versus HU	£	148,383	per QALY
IFN-α versus HU	£	2,468,015	per QALY
Imatinib versus IFN-α	£	38,411	per QALY

The independent model assumes longer survival in accelerated phase than Novartis model, which postulates a median of 6 months. The independent model runs for a total of 20 years compared to 30 years for the Novartis models. If we were to reduce the Novartis model to 20 years it would lead to an increase in the ICERs to approximately £29,000 (PFS method) and £20,000 (CR method).

The Novartis models assume 31 days of inpatient care if a patient received palliative care. The independent economic model assumes 9 days inpatient stay per cycle in blast phase. If we change the independent model to assume 12 days of inpatient care per cycle (3 months) in accelerated and blast phase then the ICER for imatinib versus IFN-α decreases to £24,396.

The Novartis models assume that once a patient experiences disease progression they receive no further active treatment, only palliation. However, this incurs considerable costs.

The Novartis and independent economic model use the same utility values for chronic phase imatinib, chronic phase IFN-α+Ara-C, and CR for imatinib and IFN-α+Ara-C. The Novartis model uses 0.8445 for chronic phase HU whereas the independent model uses 0.9, the Novartis model uses 0.5952 for both accelerated and blast phases whereas the independent model uses 0.729 for accelerated and 0.524 for blast. If the independent model is adjusted to have the same utilities as the Novartis model then the resulting ICERs are shown in Table 38. The changes make little difference to the ICER comparing imatinib and IFN-α but more difference to the ICER for IFN-α compared to HU.

Table 38 Results if independent model utilities are changed to be the same as the Novartis model

Drug		Cost per person	QALYs per person
HU	£	38,322	4.70
Imatinib	£	215,684	7.01
IFN-α	£	163,581	5.01
ICERs:			
Imatinib versus HU	£	76,709	per QALY
IFN-α versus HU	£	394,237	per QALY
Imatinib versus IFN-α	£	26,124	per QALY

The Novartis model also provides clinician estimates of utility. When these figures are used in the independent economic model the results are shown in Table 39. The resulting ICER

for imatinib versus IFN-α is slightly higher, but the most marked difference is that the ICER for IFN-α compared to HU is considerably lower.

Table 39 Results if the Novartis clinician estimates for utility are used in the independent economic model

Drug	Cost (per person/ year)		QALYs (per person/ year)
HU	£	38,322	4.41
Imatinib	£	215,684	7.01
IFN-α	£	163,581	5.09
ICERs:			
Imatinib versus HU	£	68,313	per QALY
IFN-α versus HU	£	184,022	per QALY
Imatinib versus IFN-α	£	27,199	per QALY

The independent model assumes that 30% of people progress from chronic phase to accelerated phase whereas the Novartis model postulates that 70% progress. The ICER in the independent model changes to £22,178 if the Novartis figure is used.

In conclusion the main differences between the Novartis model and the independent economic model in the resulting ICER for imatinib versus IFN-α is the modelling of survival for imatinib after 12 months, and the progression from chronic phase to accelerated and blast.

6 IMPLICATIONS FOR OTHER PARTIES

Improvements in quality of life are reported for those with CML taking imatinib, compared to IFN-α+Ara-C. In some cases, anecdotal evidence suggests that people with CML are able to return to work after switching from treatment with IFN to imatinib. The financial impact for patients and their families of treatment with imatinib is possibly lower than for those taking IFN-α . There may be productivity impacts on those of working age, both directly to the patient involved and indirectly through the impact on their family and carers.

For retired people, the impact of CML on family and carers may be reduced, although there is no empirical evidence on this issue.

The impact of imatinib on primary care services is uncertain. Remission rates associated with imatinib will possibly lead to less monitoring costs and costs of attendance. There are unlikely to be major impacts on NHS staffing levels.

Currently, approximately 10% of all patients with CML are enrolled in trials of imatinib sponsored by the pharmaceutical company which funds their treatment.

Children and the elderly have generally been excluded from pharmaceutical trials (although new trials in children are planned or under way). Imatinib is not currently licensed in the UK for children.

7 FACTORS RELEVANT TO NHS

Clinical and consumer interest in imatinib are such that uptake of imatinib is likely to be rapid. Imatinib has been given orphan drug status by the European Agency for the Evaluation of Medicinal Products (EMEA) and the Food and Drug Administration (FDA). The National Institute for Clinical Excellence recommended imatinib for second line treatment after failed IFN-α in September 2002. In December 2002 imatinib was licensed by the EMEA for first line use in the management of CML.

We have not attempted to collect and synthesise evidence regarding patients views, experiences and wishes. Such good quality evidence (if available) would be useful to help inform imatinib policy decisions.

Costs to the NHS, other than direct drug costs are difficult to predict. It is not known whether imatinib will result in less outpatient and inpatient visits while patients are undergoing therapy. It is possible that expensive PCR monitoring will become routine and bone marrow tests, radiology and blood transfusions may all increase in frequency. It is also likely that imatinib will be offered to people who would not be offered IFN-α because of potential for adverse effects.

The total cost impact on NHS budgets, in addition to the above, will depend on the number of people eligible for first line treatment with imatinib, the uptake of first line treatment with imatinib, the cost of imatinib and cost savings from avoided IFN-α therapy.

Assuming an annual incidence in England and Wales of 531, a 10% bone marrow transplant rate, 90% uptake and a dose of 400mg, the annual costs of treating all remaining patients with imatinib, IFN-α or HU are shown in Table 40, and are between £1,000,000 for HU and £10,000,000 per year for imatinib. Calculations are based on the independent economic model.

Table 40 Estimated cost of treatment with imatinib, interferon-alpha or hydroxyurea

	Assume all drug treatment with imatinib	Assume all drug treatment with IFN-α	Assume all drug treatment with HU
% of CML popn treated with drugs	90%	90%	90%
year 1	£10,378,869	£6,422,191	£1,670,511
year 2	£10,073,609	£7,127,177	£2,122,093
year 3	£8,871,058	£6,625,447	£1,966,709
year 4	£7,251,156	£5,498,471	£1,551,262
year 5	£5,410,930	£4,043,731	£1,052,829
Total	£41,985,621	£29,717,017	£8,363,404

Table 41 estimates current drug costs for the NHS and provides an estimated impact on the NHS of introducing imatinib (while accounting for the savings as a result of less IFN-α and HU use).

Two scenarios are presented. Both scenarios assume that the current cost consists of 45% of new cases of CML being offered IFN-α, 45% HU and 10% BMT. Scenario 1 gives the cost of imatinib less the current spend, assuming that 5% remain treated with IFN-α and 65% are treated with imatinib, 10% have BMT, and 20% with HU. Scenario 2 gives the cost of

imatinib less the current spend, assuming that 5% remain treated with IFN-α and 75% are treated with imatinib, 10% have BMT, and 10% with HU.

Table 41 Estimated total impact on NHS

	Current spend (45% IFN-α, 45% HU).	**Scenario 1 (65% imatinib, 5% IFN-α & 20% HU)**		**Scenario 2 (75% imatinib, 5% IFN-α & 10% HU)**	
% of CML popn treated with drugs	90%	90%		90%	
	Total £ thousands	Total £ thousands	Incremental costs (scenario 1- current spend)	Total £ thousands	Incremental costs (scenario 2 – current spend)
year 1	£4,552	£9,251	£4,699	£10,340	£5,788
year 2	£5,202	£9,160	£3,958	£10,154	£4,952
year 3	£4,833	£8,113	£3,280	£8,976	£4,143
year 4	£3,965	£6,623	£2,657	£7,335	£3,370
year 5	£2,866	£4,912	£2,054	£5,457	£2,590
Total	£21,420	£38,061	£16,641	£42,264	£20,844

The estimated current spend on treatment with IFN-α and HU alone is approximately £20,000,000. The estimated impact of scenario 1 less the current spend is around £16,000,000 and the estimated impact of scenario 2 less the current spend is approximately £20,000,000 for the first 5 years of treatment. Table 42 shows the net impact (cumulative) on the NHS over the next 5 years. Costs will be between £4 and 6 million in the first year rising to between £16 and 20 million by year 5.

Table 42 Net impact on the NHS over 5 years

	Scenario 1 Net cost £ thousands	**Scenario 2 Net cost £ thousands**
year 1	£4,699	£5,788
year 2	£8,657	£10,740
year 3	£11,938	£14,883
year 4	£14,595	£18,253
year 5	£16,641	£20,844

The estimated net impact is difficult to capture due to uncertainty regarding long-term survival with imatinib. The total prevalence of CML may rise and many of these patients will be on long-term imatinib therapy. We have not attempted to calculate the net impact on the NHS after 5 years but it is likely to be greater than the 5 year estimates assuming that prolongation of survival does occur.

8 DISCUSSION

Early results of imatinib for first line therapy are promising, although only 18 month follow-up data are currently available. Imatinib is associated with higher cytogenetic response rates, a longer median time to progression and less side-effects. No comparisons of imatinib with hydroxyurea or bone marrow transplant were found. Assuming that complete CR is causally associated with prolonged survival (which may or may not be justified), it is likely that imatinib will be associated with better outcomes than hydroxyurea and, at least in the short term, better outcomes than bone marrow transplant (for approximately the first 4 years).

Limitations of included studies

Only one RCT of imatinib compared to IFN-α+Ara-C as first line therapy is available to date, provided by Novartis.[60] Not all aspects of the trial have been available for independent scrutiny. RCTs are associated with fewer threats to internal validity when well conducted. They are potentially the best tool for answering questions of effectiveness. The current clinical question is, however, difficult to study in a rigorous RCT, due to ethical issues and patient preferences. In the Novartis study 0106[60], due to the popularity and perceived effectiveness of imatinib by patients and clinicians, there were high cross over rates to that treatment arm, and higher loss to follow-up in the IFN-α+Ara-C treatment arm. The trial was open label with no blinding, which introduces possibilities for performance and measurement bias. The study should be applicable to the UK setting, although as entry criteria were rigorous, a low risk group of patients was included. Many patients who will be seen in the clinical setting were not recruited.

Due to the lack of long-term data beyond 18 months, this assessment relies on surrogate outcomes which may not directly relate to survival.

Results of systematic reviews

Imatinib was associated higher rates of CR than IFN-α+Ara-C and lower rates of progression to accelerated or blast phases at 12 months. Overall survival was not statistically significantly different between the two groups. Withdrawal due to side-effects was slightly higher for IFN-α+Ara-C than for imatinib and cross over due to intolerance was much higher in the IFN-α+Ara-C group. Quality of life was better in the imatinib group compared to the IFN-α+Ara-C group when assessed at 1, 3 and 6 months using the FACT-BRM instrument.

IFN-α is more effective than HU in prolonging survival. Median survival across the four IFN-α versus HU studies was greater for IFN-α. However, IFN-α also has greater side-effects and much higher withdrawal rates.

Four out of the five studies comparing BMT and IFN-α showed a long-term survival advantage for BMT compared to IFN-α, but a short-term (0-4 years approximately) disadvantage. In the BMT group death due to transplant related complications ranged from 36 to 45% (median 38%).

Cost effectiveness results

The independent economic model gave estimates for the ICER of imatinib compared to IFN-α of £26,180 per QALY (ranging from £13,555 to £51,870), whereas the Novartis models

gave estimates of £18,865 to £26,850 per QALY. We were not able to model bone marrow transplant in the time available, and such an analysis would have relied heavily on speculative data. Hence we are not able to comment on potential cost-effectiveness of imatinib compared to bone marrow, and suggest this is an area where research is urgently required.

There are a number of different possible pathways for management of CML. We have modelled imatinib (1st line), IFN-α (2nd line) and mercaptopurine (blast phase) compared to IFN-α (first line) and imatinib (2nd line and blast phase). These are only two possibilities for what may occur in clinical practice. Possible alternative options include the use of combination therapy and dose reductions or escalations. To further complicate matters, BMT may be available for certain patients and optimal timing of this option is not clear. A recent paper by Goldman and colleagues[102] suggests that due to the advent of imatinib there are now two possible approaches to managing newly diagnosed CML patients for whom a suitable donor is available. Firstly, all such patients could be offered an initial trial with imatinib, with responders continuing indefinitely and non-responders proceeding to transplant. Alternatively, it may be possible to define a category of low-risk patients who could be recommended initial tranplants.[102]

This analysis describes an interesting position. IFN-α is at present considered standard therapy for people in whom BMT is not an option. However, the analysis suggestss that IFN-α itself is not a cost-effective option compared to HU, due to a combination of higher costs, a moderate increase in longevity and a considerable decrease in quality of life in many people. Strictly speaking, IFN-α should be ruled out of this analysis by extended dominance, and the ICER of relevance is that of imatinib/HU. However, HU as a comparator treatment may not be considered to be a realistic alternative to combine with imatinib to achieve extended dominance.

The complexity of possible management pathways and the incorporation of BMT have not been completely captured within the independent economic model. There is need for consensus development work in order to identify a more limited range of treatment options to model and, possibly, a need to produce cost-effective guidelines.

Assumptions, limitations and uncertainties of this review

The scope of this assessment was limited to first line treatments for adults with CML. We included only English language studies which may not be representative of the entire literature available. However, we have included a number of studies conducted in non-English speaking countries.

Due to the lack of comparative evidence for imatinib, BMT and HU we have presented indirect comparisons based on the common comparator IFN-α. Such indirect comparisons are problematic due to the likely difference in populations and should be interpreted with much caution. However, they do provide some indication of the expected difference in outcomes between the treatments.

It is currently not known whether treatment with imatinib will need to be continued indefinitely. It is thought possible that IFN-α can be stopped in some cases after several years treatment. Pegylated interferon has recently been used for the treatment of CML and it is unknown how this treatment option will compare directly to imatinib or whether it will be beneficial in combination therapy.

One of the uncertainties with this assessment is around long-term outcomes with imatinib. Currently, 18-month data is available whereas for IFN-α 10 year trial follow-up data is published. Although CR is generally agreed to correlate with survival for IFN-α, the assumption of a similar relationship for imatinib is speculative, and will partly depend on the degree of resistance to imatinib that emerges over time. Disease progression on imatinib and a failure to maintain response in blast phase is, at least partly, due to an inability to maintain BCR-ABL kinase activity, indicating resistance. The mechanisms of resistance for imatinib are not clear. It is unknown whether combination therapy (such as imatinib+IFN-α, or imatinib+ Ara-C) will help overcome disease resistance and research on this is still in the early stages. However, it is encouraging that 3-year follow-up data of imatinib as second line treatment for failed IFN-α shows that survival with imatinib remains above 90% at 3 years.[59]

The independent economic model assumes that once a patient fails imatinib by losing their CR a further CR is not possible. Although studies have demonstrated that responses are still possible with second line treatment we have taken a simpler approach to the modelling. It is likely that the impact would be negligible due to the small number of the cohort affected.

The results of this assessment are likely to be generalisable to many of those in the UK with CML. Those who the results may be less applicable to are high-risk patients, the elderly, those eligible for BMT or children. CML is rare in children but trials of imatinib are either planned or under way and effectiveness in this group will be an important future investigation.

Need for further research

Long-term follow-up data from the first and second line imatinib trials is critical in order to determine the effect on survival, duration of response and development of resistance.

Research is also needed into specific subgroups such as the high-risk patients, elderly, children or those eligible for BMT. Long term comparisons of imatinib (possibly non-randomised due to ethical and other considerations) with BMT performed in early stages of CML are important to identify if and when a survival advantage shifts from imatinib to BMT.

Imatinib is likely to be used in combination with other therapies, and detailed research is necessary to determine optimal treatment pathways.

More detailed economic studies are also required in order to aid appraisal of imatinib compared to bone marrow transplant, and in high risk patients, and to help provide cost-effective guidelines.

Further investigation of the effect of CML and imatinib on quality of life is important, especially in terms of eliciting societal values.

9 CONCLUSIONS

Imatinib appears to be more effective than IFN-α in terms of cytogenetic response and progression free survival, with fewer side-effects. Assuming that complete CR is causally associated with prolonged survival, it is likely that imatinib will be associated with better outcomes than hydroxyurea and at least in the short term better outcomes than bone marrow transplant (for approximately the first 4 years).

The ICER of imatinib compared to IFN-α was £26,180 per QALY gained and was relatively robust when subjected to a number of sensitivity analyses. This figure is similar to industry estimates of between £18,000 and £26,000 per QALY.

However there is uncertainty concerning longer term outcomes, resistance and duration of response. The place of imatinib in the management of CML, alongside BMT and in combination with other chemotherapeutic agents, remains to be established in detail. Further research and long term follow up of existing studies are needed.

10 APPENDICES

10.1 Prognostic Scores

The Sokal Score	
Score	= Exp[0.0116 (age-43.4) + 0.0345 (spleen size – 7.51) + 0.188 ([platelets/700]^2 – 0563) + 0.0887 (blasts – 2.1)]
Low risk	< 0.8
Intermediate risk	= 0.8 – 1.2
High risk	> 1.2

New prognostic score (interferon score)[24]	
New score	= 0.6666 x age [0 when age <50; otherwise 1] +0.042 x spleen size (cm below costal margin) + 0.0584 x blasts [%] + 0.0413 x eosinophils [%] + 0.2039 x basophils [0 when basophils <3%; otherwise 1] + 1.0956 x platelet count [1 when platelets < 1500 otherwise 1]) x 1000
Low risk	≤ 780
Intermediate risk	= 780-1480
High risk	> 1480

10.2 Resistance to Imatinib

Possible mechanisms for resistance to Imatinib are:

Cell intrinsic mechanisms (Cellular level)

These are changes within the cell that reduce the sensitivity of BCR-ABL to Imatinib. There is experimental evidence to support the existence of these changes:[52] cells from patients collected at various stages in the CML disease process showed a 10 fold reduction in sensitivity to Imatinib *in vitro*. Various mechanisms could account for this.

Gene amplification. This has been demonstrated in several patients who have relapsed following treatment with Imatinib. The drug may select for proliferation of clones with multiple copies of BCR-ABL in some patients.[52] Demonstrated amplification of the BCR/ABL target gene has also been noted in resistant clones of cultured cells.[54] The degree of amplification was proportional to the final selection concentration of imatinib. It has also been observed that a withdrawal of imatinib from resistant cell cultures caused the BCR/ABL level to drop.[54]

Point mutations within the kinase domain of BCR-ABL which confer resistance to Imatinib. This has been demonstrated empirically,[52] and again, selection pressure conferred by the drug may play a part.

Over-expression of the multi-drug resistance gene, which increases levels of P-glycoprotein, a cell membrane protein that pumps drugs out of the cell and lowers net intra-cellular drug concentration. This has been reported *in vitro*.[103]

Secondary genetic charges could provide signals that replace BCR-ABL as the determinant of cell proliferation[52, 53]These could be compensating mutations in other genes or other chromosomal changes (for example loss of tyrosine phosphatase activity, loss of apoptosis genes, or gain of function mutations in viability genes).[104] This has not yet been demonstrated empirically as a mechanism of resistance to imatinib.

Cellular drug metabolism or efflux

Recovery of protein tyrosine phosphorylation may be accomplished in a compensatory fashion by a mechanism not involving BCR/ABL.[54] Activation of an alternative tyrosine kinase may be a possible explanation for imatinib resistance.[103] Cells may develop methods to increase degradation or metabolism of the drug or increased efflux may be present.[104]

Cell extrinsic mechanisms (Organismal level)

Imatinib is 95% bound in plasma.

Functional sequestration of the drug. Pre-clinical studies in mice have demonstrated that alpha 1 acid glycoprotein can bind imatinib in serum and inhibit activity against BCR-ABL.[105]. Co-administration of other drugs can reduce this.

Functional inactivation of the drug through enzyme modification. This is a theoretical possibility but has not been demonstrated.

Pharmacological resistance at organismal level

This has been documented not as a lack of initial response but as a resistance following treatment with imatinib. In a study of mice resistant to imatinib, the recovered tumour cells retain the same sensitivity to imatinib as the parental cells. The mice however had a raised plasma AGP level. AGP levels may impact on the bioavailability of imatinib, especially in later stages of disease.[54]

It is likely that no single mechanism explains all resistance to imatinib, although some are more commonly seen than others. It is also possible that cellular and organismic types of resistance are complementary rather than mutually exclusive.[106] Mechanisms of resistance to imatinib may also be multifactorial.[104]

10.3 Search Strategy – STI 571 (imatinib mesylate and CML)

Updated search from 31/08/2001 –/10/2002

Databases and years searched	Date searched and search files	Number of hits (download file)
MEDLINE 20010831- 20021003 (Update codes)	Search ran on 14/10/02 Reran sti571 (saved strategy on Webspirs sti-cml-med) (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and ((((gleevec or glivec or imatinib or sti 571 or sti-571 or sti571) or (st1 571 or st1-571 or st1571 or stl571 or stl-571 or stl 571) or ((gleevec or glivec or imatinib or sti 571 or sti-571 or sti571) or (st1 571 or st1-571 or st1571 or stl571 or stl-571 or stl 571))) and (UD=20010831-20021003) and (LA=ENGLISH)) and (((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml) or ((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml))) and (UD=20010831-20021003) and (LA=ENGLISH)))	178 of which 9 CCTs
Pubmed (last 90 days)	Run on 08/10/02 gleevec OR glivec OR imatinib OR sti 571 OR sti-571 OR sti571 OR st1 571 OR st1-571 OR st1571 OR stl571 OR stl-571 OR stl 571	64
EMBASE 2001/07- 2002/09 2001/01- 2002/09	sti_emb Run on 08/10/02 ((((imatinib or glivec or gleevec) and (English in la)) or ((sti 571 or sti-571 or sti571 or st1 571 or st1-571 or st1571 or stl571 or stl-571 or stl571) and (English in la))) and ((((chronic near myel* near (leukemia or leukaemia)) or cml) and (English in la)) or (‘chronic-myeloid-leukemia’ / all subheadings))) and ((‘clinical-trial’ / all subheadings) or (‘phase-3-clinical-trial’ / all subheadings) or (‘phase-1-clinical-trial’ / all subheadings) or (‘phase-2-clinical-trial’ / all subheadings) or (‘phase-4-clinical-trial’ / all subheadings)) Saved strategy: sti-cost-emb (cost* or economic*) and (gleevec or glivec or imatinib or sti 571 or sti-571 or sti571 or st1 571 or st1-571 or st1571 or stl571 or stl-571 or stl 571) Retrieved 28	81 15
SCI 2002 English only Title	Title=sti 571 or sti571 or st1571 or st1 571 or imatinib or gleevec or glivec or stl571 or stl 571;	297 (18 downloaded)
Web of Science Proceedings 2002	Title=sti 571 or sti571 or st1571 or st1 571 or imatinib or gleevec or glivec or stl571 or stl 571	8
The Cochrane Library Issue 3 2002	sti 571 or sti571 or st1571 or st1 571 or imatinib or gleevec or glivec or stl571 or stl 571	0
NRR (National Research Register) Issue 3 2002	Saved strategy sti571_cml sti 571 or sti571 or st1571 or st1 571 or imatinib or gleevec or glivec or stl571 or stl 571 (most in combination with pegIFN)	18
ASCO – American	Sti571 or glivec or imatinib http://www.asco.org/asco/ascoMainConstructor/1,1003,_12-	30+

Society of Clinical Oncology Annual Meeting Abstracts 2002	002095,00,00.asp Includes Druker RCT first phase study of Imatinib v iFN http://www.asco.org/asco/ascoMainConstructor/1,1003,_12-002326-00_29-00A-00_18-002002-00_19-001,00.asp	
BIOSIS Limited to 2002 pub year and meeting abstracts	15/10/02 – al: sti571 or al: sti 571 or al: sti-571 or al: st1 571 or st1571 or st1-571 or al: imatinib or glivec or gleevec and al: cml or chronic myeloid leuke*mia	155 found 42 downloaded
Total references in STI571_Update database after download and deduplication		**214**

Web links

FDA web site: FDA Oncology Tools Study - Details for imatinib mesylate for Initial therapy of chronic myelogenous leukaemia See:

- http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=239
- http://www.cptech.org/ip/health/gleevec/ Information on imatinib
- The Pharmaceutical Journal http://www.pharmj.com/Editorial/20020525/news/imatinib.html

10.3.1 Search Strategy – Hydroxyurea and interferon alpha and CML

Updated search from 2001/06 to 2002/10

Databases and years searched	Date searched and search files	Number of hits (download file)
MEDLINE 2001/08-2002/10	Search run 14/10/02 Saved as hydroxy_update_med (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and ((('Leukemia-Myeloid-Chronic' / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((hydroxyurea and (UD=20010831-20021003) and (LA=ENGLISH)) or (('Hydroxyurea-' / all subheadings in MIME,MJME) and (UD=20010831-20021003) and (LA=ENGLISH))))	7
Pubmed (last 90 days)	hydroxyurea and chronic myeloid leukemia	3
EMBASE 2001/07-2002/09	Search run 15/10/02 Saved as cml_hydroxy_emb ((explode 'clinical-trial' / all subheadings) and (((hydroxyurea) or ('hydroxyurea-' / all subheadings)) and ((cml or chronic myeloid leuk*emia) or ('chronic-myeloid-leukemia' / all subheadings)))) and (LA=ENGLISH)	26
ISI Science Citation Index 2001-2002	Search run 16/10/02 hydroxyurea and (cml or chronic myeloid leuk*emia)	15
The Cochrane Library Issue 3/2002	Searched 16/10/02 Saved as cml_hyd Limited to 2001-2002 and included new updates	4
NRR Issue 3/2002	Searched 16/10/02 Saved as cml_hydroxy (overlap with bmt & IFN)	31

Biosis 2001-2002	((al: (hydroxyurea)) and al: (interferon*)) and al: (chronic myeloid leukemia)	5
Total references in database after deduplication		**60**

10.3.2 Search Strategy – Bone marrow transplant and interferon alpha and CML

New search 14/10/02 All years

Databases and years searched	Date searched and search files	Number of hits (download file)
MEDLINE 1966-2002/10	Date searched: 14/10/02 Strategy saved on Webspirs – IFN_BMT_med (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and ((('Leukemia-Myeloid-Chronic' / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((interferon*) or (explode 'Interferon-alpha' / all subheadings in MIME,MJME)) and (('Bone-Marrow-Transplantation' in MIME,MJME) or (bone near marrow near transplant*) or (bmt)))	77
Pubmed (last 30 days)	Date searched: 14/10/01 ((('Leukemia-Myeloid-Chronic' / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((interferon*) or (explode 'Interferon-alpha' / all subheadings in MIME,MJME)) and (('Bone-Marrow-Transplantation' in MIME,MJME) or (bone near marrow near transplant*) or (bmt)))	31
EMBASE 1980 – 2002/09	Date searched: 15/10/02 (('clinical-trial' / all subheadings) or ('phase-3-clinical-trial' / all subheadings) or ('phase-1-clinical-trial' / all subheadings) or ('phase-2-clinical-trial' / all subheadings) or ('phase-4-clinical-trial' / all subheadings)) and ((((bone marrow transplant*) or (bmt) or ('bone-marrow-transplantation' / all subheadings)) and ((interferon*) or ('alpha-interferon' / all subheadings))) and ((((chronic near myel* near (leukemia or leukaemia)) or cml) and (English in la)) or ('chronic-myeloid-leukemia' / all subheadings)))	129
ISI Science Citation Index All years 1981-2002	Date searched 16/10/02 interferon* and (bmt or bone marrow transplant*) Title only	87
The Cochrane Library Issue 3/2002	Searched 16/10/02 Saved as cml_bmt	12
NRR Issue 3/2002	Searched 16/10/02 Saved as cml_bmt_ifn	42
Biosis - All years Meeting Abstracts	al: bone marrow transplant* and al: interferon* and al: chronic myeloid leukemia	39
Total records in Reference Manager d/b		**349**

10.4 Excluded studies

10.4.1 Imatinib

The following studies which were included in the previous NICE assessment report, were excluded for this report

- Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C *et al*. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;346(9):645-52. (Not first line treatment of CML)
- Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG *et al*. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: Results of a phase II study. *Blood* 2002;99(10):3530-9. (Not first line treatment of CML)
- Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti PC, Guilhot F *et al*. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: Results of a phase 2 study. *Blood* 2002;99(6):1928-37. (Not first line treatment of CML)

The following were excluded from the update search at full text stage

- Barbany G, Hoglund M, Simonsson B. Complete molecular remission in chronic myelogenous leukemia after imatinib therapy. *N Engl J Med* 2002;347(7):539-40. (Not first line treatment of CML)
- Feng L, Drummond M, Cervantes F, Holyoake T, Kaeda J, S. Molecular remission following treatment with STI571 for chronic myeloid leukaemia: A report from the UK571 study group. British Society for Haematology 2002;42nd Annual Scientific Meeting, Brighton, UK, April#15-18,#2002; *Br J Haematol* [print]#117(Supplement#1):4-science. (Preclinical/ biological/ genetic studies)
- Fruehauf S, Toplay J, Schad M, Ho AD, Zeller WJ. Rationale for combination therapy of chronic myelogenous leukemia with imatinib and irradiation or alkylating agents: implications for pretransplant conditioning. *International Society for Experimental Hematology Annual Meeting* 2002;Abstract no. 224. (Preclinical/ biological/ genetic studies)
- Huntly JP, Guilhot F, Byrne J, Hennig E, Muller C, Niederwieser D *et al*. Treatment with Imatinib appears to improve the poor prognosis associated with derivative chromosome 9 deletions in patients with CML. *European Hematology Association (EHA) Annual Meeting* 2002;Abstract Number 0978. (Not first line treatment of CML)
- Jones GR, Johnson FL, Rosamilia M, Druker BJ. Activity and Safety of Gleevec (STI-571), an abl Tyrosine Kinase Inhibitor in Children with Philadelphia Chromosome-Positive Leukemias. *American Society for Hematology Conference* 2001;Abstract No 2475. (Children)
- Jorgensen H. Will drug combinations effectively eradicate quiescent leukaemic stem cells in Chronic Myeloid Leukaemia (CML)?31st Annual Meeting of the International Society for Experimental Hematology, Montreal, Quebec, Canada, July 05-09,#2002; *Exp Hematol* (Charlottesville):73. (Preclinical/ biological/ genetic studies)
- Kantarjian H, Cortes J, O'Brien S, Giles FJ, Thomas D, Faderl S *et al*. High rates of early major and complete cytogenetic responses with imatinib mesylate therapy given at 400mg or 800mg orally daily in patients with newly diagnosed philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (PH+CML-CP).

American Society of Clinical Oncology Scientific Meeting 2002;Abstract No. 1043. (Abstract only)

- Kantarjian HM, Cortes J, O'Brien S, Giles F, Thomas D, Garcia-Manero G *et al*. Imatinib Mesylate (STI571) Therapy of Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Early Chronic Phase (PH+CML Early CP). *American Society for Hematology Conference* 2001;Abstract No. 577. (Abstract only)
- Korycka A, Robak T. The comparison of influence of STI571 used alone or in combination either with 2-chlorodeoxyadenosine or fludarabine on the normal and chronic myelogenous leukemia progenitor cells in vitro. *European Hematology Association (EHA) Annual Meeting* 2002. (Preclinical/ biological/ genetic studies)
- Marin D, Marktel S, Bua M, Armstrong L, Goldman JM, Apperley JF *et al*. The use of imatinib (STI571) in chronic myeloid leukemia: some practical considerations. *Haematologica* 2002;87(9):979-88. (Not first line treatment of CML)
- O'Brien S, G, Vallance S, E, Craddock C, M. Pegintron and STI571 combination evaluation study (PISCES) in chronic phase chronic myeloid leukaemia. British Society for Haematology 2002;42nd Annual Scientific Meeting, Brighton, UK, April#15-18,#2002; *Br J Haematol* [print]#117(Supplement#1):3-4. (No control group)
- O'Dwyer ME, Mauro MJ, Aust S, Kuyl J, Paquette R, Sawyers C *et al*. Ongoing evaluation of the combination of Imatinib mesylate (Glivec TM) with low dose interferon-alpha for the treatment of chronic phase CML. *European Hematology Association (EHA) Annual Meeting* 2002. (No control group)
- Schad M, Toplay J, Zeller W, Fruehauf S. Imatinib in combination with 17-allylamino-17-dexethoxy-geldanamycin (17-AAG) for treatment of chronic myelogenous leukemia. *European Hematology Association (EHA) Annual Meeting* 2002;Abstract no. 1005. (Preclinical/ biological/ genetic studies)
- Topaly J, Schad M, [a]. Imatinib in combination with 17-allylamino-17-demethoxy-geldanamycin (17-AAG) for treatment of chronic myelogenous leukemia.31st Annual Meeting of the International Society for Experimental Hematology, Montreal, Quebec, Canada, July 05-09,#2002; Experimental Hematology(Charlottesville):72. (Preclinical/ biological/ genetic studies)
- Trabacchi E, Bassi S, Saglio G, Rege-Cambrin G, Bonifazi F, De Vivo A *et al*. Pegylated recombinant interferon alpha2b (Pegintron) associated with imatinib mesylate (Glivec) in Ph chronic myeloid leukaemic (CML) in early chronic phase: a phase II study of the ICSG on CML. *European Hematology Association (EHA) Annual Meeting* 2002. (No control group)
- Vasilica M. The use of Glivec in chronic myeloid leukemia: Report of 10 cases in a single institution.31st Annual Meeting of the International Society for Experimental Hematology, Montreal, Quebec, Canada, July 05-09,#2002; *Exp Hematol* (Charlottesville):96. (Not first line treatment of CML)

10.4.2 Interferon alpha versus hydroxyurea

The following studies which were included in the previous NICE assessment report, were excluded for this report

- Shepherd PC, Richards SM, Allan NC. Progress with interferon in CML--results of the MRC UK CML III study. *Bone Marrow Transplant* 1996;17 Suppl 3:S15-S18. (More than 25% of HU group received an alternative treatment)
- Ohnishi K, Tomonaga M, Kamada N, Onozawa K, Kuramoto A, Dohy H *et al*. A long term follow-up of a randomized trial comparing interferon- alpha with busulfan for chronic myelogenous leukemia. *Leuk Res* 1998;22/9(779-786)):-786. (More than 25% of HU group received an alternative treatment)

No articles were excluded from the update search at full text stage as none were identified as being relevant.

10.4.3 Interferon alpha versus bone marrow transplant

The following were excluded from the search at full text stage

- Baccarani M. A prospective study of alpha-interferon and autologous bone marrow transplantation in chronic myeloid leukemia. *Br J Haematol* 1996;93:264. (Not comparative study- case series)
- Gale RP, Park RE, Dubois RW, Herzig GP, Hocking WG, Horowitz MM *et al*. Delphi-panel analysis of appropriateness of high-dose therapy and bone marrow transplants in chronic myelogenous leukemia in chronic phase. *Leuk Res* 1999;23(9):817-26. (Patients are not in chronic phase CML)
- Guilhot F, Sobocinski K, Guilhot J, Zhang M, Giralt S, Harousseau JL *et al*. Comparison of HLA-identical sibling bone marrow transplants (BMT) versus interferon plus cytarabine (IFN/Ara-C) for chronic myelogenous leukemia (CML) in chronic phase (CP). *Blood* 2000;96(11):2343. (Abstract only)
- Hehlmann R, Berger U, Hochhaus A, Reiter A, Pfirrmann M, Hasford J *et al*. Genetic randomization of allogeneic BMT vs drug treatment in chronic myelogenous leukemia: The German CML study III. *?* 2000;42nd Annual Meeting of the American Society of Hematology, San Francisco, California, USA, December 01-05,#2000; *Blood* [print]#96(11 Part#1):141a. (Abstract only)
- Hehlmann R, Berger U, Hochhaus A, Reiter A, Pfirrmann M, Hasford J *et al*. Randomized comparison of allogeneic BMT and IFN-based therapy in chronic myeloid leukemia (CML). Annual Meeting of the German and Austrian Society for Hematology and Oncology, Graz, Austria, October 2000;21-25,#2000; *Onkologie* [print]#23(Sonderheft#7):89. (Abstract only)
- Ohnishi K, Ino T, Kishimoto Y, Usui N, Shimazaki C, Ohtake S *et al*. Multicenter prospective study of interferon-alpha versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: An interim analysis of the Kouseisho leukemia study group. *Blood* 2001;98(11):1468. (Duplicate publication)
- Ohnishi K. Multicenter prospective study of interferon-alpha versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: An interim analysis of the Kouseisho leukemia study group. *?* 2001;43rd Annual Meeting of the American Society of Hematology, Part#1, Orlando, Florida, USA, December 07-11,#2001; *Blood* [print]#98(11 Part #1):348a. (Duplicate publication)
- Silver RT, Woolf SH, Hehlmann R, Appelbaum FR, Anderson J, Bennett C *et al*. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: Developed for the American Society of Hematology. *Blood* 1999;94(5):1517-36. (Guideline, studies included separately)
- Tura S, Russo D, Fanin R, Zuffa E, Patriarca F, Fiacchini M *et al*. Prognostic factors in chronic myeloid-leukemia - relationship with interferon and bone-marrow transplantation. *Leuk Lymphoma* 1993;11:67-71. (Duplicate publication)
- Tura S. Monitoring the effect of allogeneic bone marrow transplantation (BMT) and of alpha-interferon (IFN) in chronic myeloid leukemia. A national prospective study in Italy. *Blood* 1996;88(10):2717. (Duplicate publication)

10.5 Quality assessment of QoL measurement in the imatinib versus interferon alpha plus ara-C trial

Criteria are taken from a systematic review by Clark and colleagues.[65]

Quality criteria	Comments
QoL definition	Not explicit, although the trial states that side-effects can have a debilitating effect on QoL
Reasons for selecting the instrument	FACT-BRM- used in clinical trials, contains general domains as well as treatment specific modules and has been validated. The version used here was IFN defined, which may bias in favour of imatinib. GRC scale- assist with interpretation of QoL scores EQ-5D- to obtain utility measures for use in the economic analysis
Domains	FACT-BRM- physical well-being, functional well-being, social well-being, emotional well-being and the impact of biological response modifiers on physical and emotional/cognitive functioning GCR scale- measures how patients rated their change in QoL since their previous visit on a 5 point scale from very much better to very much worse (completed for 6 questions each relating to a FACT-BRM domain)
Single composite score	FACT-BRM- The 27 items make up subscales that match each domain. The score is adjusted for incomplete data using a pattern-mixture technique.
Separate global rating	Yes
Supplemental patient comments	No additional patient comments were incorporated
Distinguishes overall QoL from health related QoL	Uncertain
Rating of importance	The analyses was performed using standard techniques for the FACT-BRM, there is no indication that important items were identified and ranked according to personal value in this study
Relevance of items to patients	There is no demonstration in this study, or reference to previous studies that the included items were relevant to patients in this study
Relevance of items from clinical experience	The treatment specific subscales (impact of biological response modifiers on physical and emotional/cognitive functioning) were thought to be the most likely to be affected by drug therapy
Reliability in current or previous studies	The study report states that the FACT-BRM is a “fully validated instrument”
Criterion or construct validity in current or previous studies	The analysis involved recalculation of “rasch” scores which provided supplemental evidence of the validity of the FACT-BRM. It does not appear that the instrument was compared to a gold standard measure (criterion validity).
Responsiveness	There was evidence of statistically significant changes when changes of treatment occurred. GRC scale- score used to calibrate the FACT-BRM measure in a subset of patients form the USA.
Interpretability	A change of 5 points on the FACT-BRM was said to be clinically significant according to a report on clinically relevant differences. The FACT-BRM scores were also calibrated using the GRC scores obtained from the same population. There is also the possibility of informative censoring, because patients are censored for progression or loss of response, which are related to prognosis.
Acceptability	The response rate for the quality of life measurement was moderate, with 80% of the imatinib group being assessed at 12 months and 59% of the IFN-α+Ara-C group.
Feasibility	Uncertain
Standardisation	There are published manuals that provide instructions regarding the analysis of FACT-BRM data

10.6 Data extraction tables

Imatinib

Reference and Design	Intervention	Patients	Outcome measures
Bolton & Gathmann, 2002 *Date of recruitment*: June 2000 to Jan 2002[8] *Country* Multi-centre (16 countries) *Study design:* RCT	*Intervention:* Imatinib *Comparison:* IFN-α + Ara-C *Previous treatment:* HU and/or anagrelide *Intervention dose, timing and route*: 400 mg/day oral *Comparison dose, timing and route*: Target dose of 5MU/m2/day IFN-α with maximum dose of 40mg per day for 10 days per month of Ara-C *Rules for dose escalation:* Imatinib: increased to maximum of 400mg 2Xper day for patients who failed to achieve CHR in 3 months or minor CR in 12 months of for patients who lose a major CR. IFN-α+Ara-C: Dose escalated to maximum 5MU and 40mg/day if tolerated. *Concurrent treatments:* HU, leukopheresis, allopurinol and anagrelide permitted	*Total number:* 1106 *Intervention:* 553 *Comparison:* 553 *Disease point:* Chronic phase philadelphia +ve *Time since diagnosis:* Within 6 months of diagnosis *Inclusion criteria:* age 18-70, enrolled within 6 months of diagnosis, previously untreated, Ph+CML, no evidence of extramedullary involvement (except spleen/ liver) *Exclusion criteria:* Patients in who BMT is indicated and available, ECOG status ≥3, uncontrolled medical problems, HIV, undergone major surgery in previous 4 weeks, pregnant, breastfeeding, history of another malignancy within past 5 years, non compliant/potentially unreliable patients. *Participant characteristics:* Imatinib: median age 50 years, male:female ratio 342:211, Sokal low 53%, int 29% and high 19% IFN-α+Ara-C: median age 51 years, male:female ratio 310:243, Sokal low 48%, int 30% and high 22%	*Outcome measures used:* Progression free survival, quality of life, CR, HR, overall survival, adverse events *Length of follow-up:* Median 14 months for imatinib group and 13 months for IFN-α+Ara-C group

Results

Outcome	Imatinib	IFN+Ara-C	P value
Rate of CHR	94.6%	76.5%	<0.001
Rate of major CR	82.6%	39.8%	<0.001
Rate of CCR	67.8%	19.9%	<0.001
Survival without progression (12 months)	97.2%	90.3%	<0.001
Survival without acc or blast phase (12 months)	98.5%	93.1%	<0.001
Overall survival rate	98.9%	97.9%	NS

218/553 (39%) of the IFN-α+Ara-C group crossed over to the other treatment compared to 7/553 (1%) of the imatinib group.

51/553 (9%) of the imatinib group discontinued treatment compared to 170/553 (31%) of the IFN-α+Ara-C group. Reasons for discontinuing included adverse events, unsatisfactory therapeutic effect, no longer required study drug (BMT), protocol violation, patient withdrew consent, loss to follow-up administrative problems and death.

Methodological comments

Proper randomisation? Uncertain, performed by a central independent party, stratified by country, but method not specified
Allocation concealment? Yes
Groups similar at baseline? Yes for age, gender, weight, ECOG status, previous treatment with HU, Sokal scores
Eligibility criteria stated? Yes
Outcome assessors blinded? No
Providers of care blinded? No
Patients blinded? No
Point estimate and measure of variability reported? Yes
Power calculation performed at study design? Yes
All patients accounted for? Yes
Analysis performed on ITT basis? Yes

Interferon alpha versus hydroxyurea

Reference and Design	Intervention	Patients	Outcome measures
Benelux[5], 1998 *Date of recruitment*: 1987 *Country* Belgium, The Netherlands and Luxembourg *Study design:* RCT	*Intervention:* IFN α 2b *Comparison:* HU *Previous treatment:* HU *Intervention dose, timing and route*: 3MU 5days/week subcutaneous *Comparison dose, timing and route*: Not stated, oral *Rules for dose escalation:* HU adjusted to keep WBC 5015x10^9 /L *Concurrent treatments:* HU	*Total number:* 195 *Intervention:* 100 *Comparison:* 95 *Disease point:* Chronic *Time since diagnosis:* Newly diagnosed *Inclusion criteria:* Newly diagnosed, untreated, aged >18, adequate hepatic and renal function *Exclusion criteria:* Abnormalities other than Ph+, not Ph+/BCR-ABL *Participant characteristics:* IFN-α: median age 55.7 (range 20-83), male:female ratio 58:42, Sokal score low 29%, int 43%, high 28% HU: median age 56.4 (27-84), male:female ratio 53:42, Sokal score low 30%, int 33%, high 37%	*Outcome measures used:* HR, CR survival, WBC *Length of follow-up:* Median 51 months, for living patients 66 months

Results
Survival at 1-year was 98% for the IFN-α group compared to 97% for the HU group. Complete HR was 62% for the IFN-α group and 38% for the HU group. Complete CR was 9% for the IFN-α group and 0% for the HU group. Partial CR was 7% and major CR was 16% in the IFN-α group compared to 2% partial CR and 2% major CR in the HU group.
In the IFN-α group 24% of patients withdrew due to adverse effects compared to 4% in the HU group.

Methodological comments
Proper randomisation? Uncertain
Allocation concealment? Uncertain
Groups similar at baseline? Yes
Eligibility criteria stated? Yes
Outcome assessors blinded? No
Providers of care blinded? No
Patients blinded? No
Point estimate and measure of variability reported? Yes
Power calculation performed at study design? Yes
All patients accounted for? Yes
Analysis performed on ITT basis? Yes

Reference and Design	Intervention	Patients	Outcome measures
Broustet[6] 1991 *Date of recruitment:* 1990 *Country* France *Study design:* RCT	*Intervention:* IFN α 2b *Comparison:* HU *Previous treatment:* Leukopheresis *Intervention dose, timing and route*: 4MU daily, subcutaneous *Comparison dose, timing and route*: Not stated, oral *Rules for dose escalation:* HU according to WBC, IFN-α dose reduced if adverse effects *Concurrent treatments:* Not stated	*Total number:* 58 *Intervention:* 24 *Comparison:* 26 *Disease point:* Chronic *Time since diagnosis:* Less than 3 months *Inclusion criteria:* Ph+CML, no previous treatment (except leukopheresis), less than 3 months after diagnosis, aged>18 years *Exclusion criteria:* Karyotypic abnormalities other than Ph+, patients who may benefit from an allograft *Participant characteristics:* IFN-α: median age 55.6±10.6, male:female ratio 15:9, Sokal score low 29.2%, int 50%, high 20.8% HU: median age 58.6±7.1, male:female ratio 16:10, Sokal score low 26.9%, int 46.2%, high 26.9%	*Outcome measures used:* HR, CR, adverse effects *Length of follow-up:* Not stated
Results A partial HR was achieved by 67% of the IFN-α group and by 88% of the HU group. A complete CR was achieved by 7% of the IFN-α group and by none of the HU group. A partial CR was achieved by 46% and a major CR by 53% of the IFN-α group compared to 31% partial CR and 31% major CR in the HU group. 25% of patients in the IFN-α group withdrew due to side-effects compared to 4% of the HU group.			
Methodological comments *Proper randomisation?* Yes, centralised randomisation list, equilibrated every 4 patients *Allocation concealment?* Uncertain *Groups similar at baseline?* Yes *Eligibility criteria stated?* Yes *Outcome assessors blinded?* No *Providers of care blinded?* No *Patients blinded?* No *Point estimate and measure of variability reported?* No *Power calculation performed at study design?* No, uncertain that study had sufficient power *All patients accounted for?* Yes *Analysis performed on ITT basis?* No			

Reference and Design	Intervention	Patients	Outcome measures
Hehlmann[78], 1994 *Date of recruitment:* 1983 *Country* Germany *Study design:* RCT	*Intervention:* IFN α 2a or 2b *Comparison:* HU *Previous treatment:* None *Intervention dose, timing and route*: 5MU daily subcutaneous *Comparison dose, timing and route*: HU 40mg/kg daily oral *Rules for dose escalation:* Rules for dose change/ stop. *Concurrent treatments:* Not stated	*Total number:* 327 *Intervention:* 133 *Comparison:* 194 *Disease point:* Chronic *Time since diagnosis:* Newly diagnosed *Inclusion criteria:* Newly diagnosed, not pretreated, chronic phase. Also 6 of : unexplained fatigue, wt loss> 10% in 6 months, fever of more than 38.5C on 5 consecutive days, organomegaly related symptoms, leukocytes >50X10^9/L and or thrombocytosis> 1X10^{12}/L *Exclusion criteria:* Lack of consent, living overseas, psychiatric problems, language barriers assessed as too difficult to keep to protocol *Participant characteristics:* IFN-α: median age 47.4 (range 18-85), male:female ratio 88:45, Sokal score low 27.1%, int 35.3%, high 37.6% HU: median age 46.9 (15-84), male:female ratio 98:96, Sokal score low 29.4%, int 33.5%, high 37.1%	*Outcome measures used:* HR, CR survival, adverse effects *Length of follow-up:* Not clear, "3 years after last patient randomised"
Results One-year survival was 96% in the IFN-α group and 96% for HU. Complete HR was 31% for IFN-α and 39% for HU. Partial HR was 52% for IFN-α and 51% for HU. Major HR was 83% for IFN-α and 90% for HU. Complete CR was 5% for IFN-α and 1% for HU. Partial CR was 2% for IFN-α and 1% for HU. Major CR was 7% for IFN-α, and 2% for HU. 24% of the IFN-α group and 1% of the HU group withdrew due to side-effects.			
Methodological comments *Proper randomisation?* Yes, using Efron lists, stratified for hospitals, randomised centrally by phone *Allocation concealment?* Uncertain *Groups similar at baseline?* Yes *Eligibility criteria stated?* Yes *Outcome assessors blinded?* No *Providers of care blinded?* No *Patients blinded?* No *Point estimate and measure of variability reported?* Yes *Power calculation performed at study design?* Yes *All patients accounted for?* Yes *Analysis performed on ITT basis?* Yes			

Reference and Design	Intervention	Patients	Outcome measures
Italian Cooperative Study Group on CML[21], 1998 *Date of recruitment:* 1986 *Country* Italy *Study design:* RCT	*Intervention:* IFN α *Comparison:* HU/BU *Previous treatment:* None *Intervention dose, timing and route*: 9MU daily subcutaneous *Comparison dose, timing and route*: HU/BU not stated, oral *Rules for dose escalation:* Not stated *Concurrent treatments:* HU, BU	*Total number:* 322 *Intervention:* 218 *Comparison:* HU/BU 104 *Disease point:* Chronic *Time since diagnosis:* Not stated *Inclusion criteria:* Ph+ CML in first chronic phase, minimal pretreatment (<100mg BU or <50g HU) or none *Exclusion criteria:* >70 years, accelerated or blast phase, any associated disorder that could influence treatment or its toxicity *Participant characteristics:* IFN-α: age not stated, male:female ratio not stated, Sokal score not stated HU/BU: age not stated, male:female ratio not stated, Sokal score not stated	*Outcome measures used:* CR survival, adverse effects *Length of follow-up:* Living patients 95-129 median 112 months
Results There was 95% 1-year survival rates for the IFN-α group compared to 96% for the HU/BU group. Neither group reported any patients with major HR. 4% of the IFN-α group experienced complete CR compared to 0% of the HU/BU group. There was 2% partial CR and 6% major CR in the IFN-α group compared to 1% partial CR and 1% major CR in the HU/BU group. 18% of the IFN-α group withdrew due to side-effects.			
Methodological comments *Proper randomisation?* Uncertain, allocation 2 IFN-α: 1 HU/BU *Allocation concealment?* Uncertain *Groups similar at baseline?* No *Eligibility criteria stated?* Yes *Outcome assessors blinded?* No *Providers of care blinded?* No *Patients blinded?* No *Point estimate and measure of variability reported?* Yes *Power calculation performed at study design?* Not stated *All patients accounted for?* Yes *Analysis performed on ITT basis?* Yes			

Interferon alpha versus bone marrow transplant

Reference and Design	Intervention	Patients	Outcome measures
Gale *et al.*, 1998 [9] *Date of recruitment*: Patients diagnosed between 1983 and 1991 *Country* International, multicentre *Study design*: Non randomised comparative study	*Intervention:* non-T-cell depleted, HLA-identical sibling bone marrow transplant *Comparison:* HU or IFN-α *Previous treatment:* IFN-α±HU (n=131), or HU (n=417) *BMT preconditioning:* IFN-α with or without HU *IFN-α/HU dose, timing and route*: IFN-α 5MU daily subcutaneous, HU 40mg/kg daily oral *Rules for dose escalation:* Rules for dose change/ stop *Concurrent treatments:* Post transplant methotrexate and cyclosporine for GVHD prophylaxis	*Total number:* 744 *Intervention:* 548 *Comparison:* 196 *Disease point:* Chronic *Time since diagnosis:* Median time from diagnosis to transplant 10.1 (range 2 to 84) months *Inclusion criteria:* ≥15 and ≤55 years of age. *Exclusion criteria:* Patients with >10% circulating blasts at diagnosis (IFN-α/HU group only) *Participant characteristics:* BMT: median age 35 (range 15-54) years, male:female ratio 331:217, Sokal score low 41%, int 37%, high 22% IFN-α/HU: median age 41 (range 15-55) years, male:female ratio 119:77, Sokal score low 37%, int 42%, high 21%	*Outcome measures used:* Survival *Length of follow-up:* BMT: Median 51.6 months IFN-α: Median 78 months

Results

Adjusted probability of survival after diagnosis (adjusted for time to transplant, age, sex, spleen size and year of diagnosis):

	BMT group RR of Death	IFN/HU group RR of Death
Year diagnosis ≥88	0.58 (p=0.003)	NS
Spleen size ≥10cm	NS	2.11 (p<0.001)
Female sex	0.65 (p=0.02)	0.63 (p=0.03)
Age>35 years	1.14 (p=0.04)	NS

NS= not statistically significant, RR= relative risk, BMT= bone marrow transplant, IFN-α= Interferon alpha, HU= Hydroxyurea

The 7-year probability of survival was 58% in the BMT group (95%CI 50% to 65%) compared to 32% in the IFN-α/HU group (95%CI 22% to 44%).

There was a statistically significant survival advantage for HU/IFN-α in the first 2.5 years after diagnosis, and a significant advantage for people undergoing BMT after 5.5 years (survival was similar in years 2.5 to 5.5). When considering only the 331 people who received a transplant within 1 year of diagnosis, there was a survival advantage for IFN-α/HU in the first 1.8 years and for BMT after 4.8 years. Survival in the BMT group did not differ according to Sokal risk group. For the IFN-α/HU group low risk patients had significantly longer survival than intermediate or high-risk patients.

Methodological comments
Proper randomisation? No
Allocation concealment? Not applicable
Groups similar at baseline? No, time to intervention was different but adjusted for using left-truncated Cox regression model was used. There were also differences in baseline patient characteristics (age, sex, spleen size, & blasts and year of diagnosis), which were adjusted using covariates in the Cox model and by stratifying analysis by Sokal score.
Eligibility criteria stated? Yes
Outcome assessors blinded? No, but outcome is objective
Providers of care blinded? Not possible
Patients blinded? No
Point estimate and measure of variability reported? Yes
Power calculation performed at study design? No
All patients accounted for? Yes
Analysis performed on ITT basis? Not applicable

Reference and Design	Intervention	Patients	Outcome measures
Gaziev *et al.*, 2002[10] *Date of recruitment*: April 1981 to Feb 2000 *Country* Italy *Study design*: Non-randomised comparative study	*Intervention: BMT* (HLA identical sibling donors, identical twin or HLA phenotypically matched) *Comparison:* Chemotherapy or IFN-α *Previous treatment:* Not stated *BMT preconditioning:* Either cyclophosphamide (CY) plus single-dose total body irradiation at 10 Gy (CYTBI) or BU plus CY (BUCY) *Comparison dose, timing and route*: patients received different doses *Rules for dose escalation:* Not stated *Concurrent treatments:* Prophylactic antibiotics, acyclovir, amphotericin B and trimethoprim/ sulfamethoxazole.	*Total number:* 175 *Intervention:* 105 (HLA identical sibling donors 102, identical twins 2, HLA-identical relative donor 1) *Comparison:* 70 *Disease point:* At commencement of trial 88 (84%) people were in chronic phase and 17 (16%) advanced phase; *Time since diagnosis:* BMT: <12 months 52%, 12-36 months 34%, >36 months 14%. Year of diagnosis <1990 63% for BMT and 67% for non-BMT *Inclusion criteria:* Patients with CML *Exclusion criteria:* None stated *Participant characteristics:* Chronic phase BMT: median age 31 (range 10-53), male:female ratio 38:50, Sokal score low 59%, int 32%, high 9% Non-BMT: median age 43 (range 14-55), male:female ratio 45:25, Sokal score low 68%, int 29%, high3%	*Outcome measures used:* Survival, toxicity, relapse, GVHD *Length of follow-up:* Median for IFN-α 46.8 months (range 12-144)
Results 4/88 patients in the BMT group died before 21 days. Of the BMT patients 38/105 (36%) developed GVHD grade 2-4 and 23/105 (22%) grade 3-4. 70/105 (67%) BMT patients developed gram-/+ infections, 33% fungal infections with 24% candida species. Overall 51/105 (49%) patients died, 26/105 (25%) within 100 days of transplant. Relapse for those having a BMT occurred in 12/88 (14%) chronic phase and 4/17 (24%) advanced phase patients. The estimated 10-year survival in patients receiving BMT in chronic phase was 56% (range 47% to 68%) and was significantly higher than chemotherapy at 10% (range 7% to 24%) and IFN-α at 33% (range 16% to 54%). Median survival for IFN-α was 7 years and 5 years for chemotherapy (still not reached for BMT).			
Methodological comments *Proper randomisation?* No *Allocation concealment?* Not applicable *Groups similar at baseline?* The BMT and non-BMT groups were matched for clinical and haematological features including Sokal score (but excluding age and gender). Groups were not similar for age and gender with the BMT group being younger with more females. *Eligibility criteria stated?* No *Outcome assessors blinded?* Not stated although some outcomes were objective *Providers of care blinded?* Not possible *Patients blinded?* Not possible *Point estimate and measure of variability reported?* Yes *Power calculation performed at study design?* No *All patients accounted for?* Yes *Analysis performed on ITT basis?* Yes stated although not strictly followed			

Reference and Design	Intervention	Patients	Outcome measures
Italian Cooperative, 1999[79] *Date of recruitment*: From Jan 1984 to Dec 1991 *Country* Italy *Study design*: Cohort study	*Intervention:* autologous BMT (twin, HLA identical sibling with or without T-cell depletion, Related donor partially HLA matched, or unrelated donor HLA matched) *Comparisons:* Conventional chemotherapy or IFN-α *Previous treatment:* BMT patients were initially treated with HU or IFN-α. Comparison groups were previously untreated *BMT preconditioning:* Total body irradiation and cyclophosphamide ± BU, GVHD prophylaxis *Comparison dose, timing and route*: IFN-α 9MU/day, HU dose not predetermined *Rules for dose escalation:* IFN-α escalated when patients progress *Concurrent treatments:* Cyclosporine and/or methotrexate (also given before treatment)	*Total number: 840* *Intervention:* 181/840 (22%) went on to have a BMT (HLA-identical sibling donor 153, identical twins 1, HLA-matched relative donor 9, HLA-matched unrelated donor 18) *Comparison:* 659/840 (78%) did not go on to have a BMT *Disease point:* All chronic phase when registered *Time since diagnosis:* Mean time from registration for BMT was 15.1 months (±10.4) *Inclusion criteria:* Philadelphia chromosome positive CML *Exclusion criteria:* patients older than 56 years, patients previously treated for CML. *Participant characteristics:* <u>BMT</u> median age 32 years, male:female ratio 71:49, Sokal score low 49%, int 29%, high 22% <u>IFN-α</u> median age 41.5 years, male:female ratio 190:132, Sokal score low 50%, int 27%, high 23% <u>Chemotherapy</u> median age 42 years, male:female ratio 192:145, Sokal score low 45%, int 32%, high 19%	*Outcome measures used:* HR, CR, survival, leukaemia-free survival and relapse *Length of follow-up:* Until June 1997
Results In the chemotherapy group 62% had a complete HR and 60% in the IFN-α group. Overall cytogenetic response was 4% for chemotherapy and 35% for IFN-α. <u>Based on 120 who underwent standard alloBMT</u> For allo-BMT patients 43/120 (36%) died and 15/120 (13%) relapsed. At 10 years the overall survival rate was 55% (95%CI 45% to 65%) for BMT compared to 32% (95%CI 26% to 39%) for IFN-α and 18% (95%CI 14% to 22%) for chemotherapy. Median survival was not yet reached in BMT group and was 72 months in IFN-α group and 54 months in the chemotherapy group.			
Methodological comments *Proper randomisation?* No *Allocation concealment?* Not applicable *Groups similar at baseline?* No, those undergoing BMT were significantly younger. Groups had similar risk scores and blood profiles. *Eligibility criteria stated?* Yes *Outcome assessors blinded?* Not stated, although some outcomes are objective *Providers of care blinded?* Not possible *Patients blinded?* Not possible *Point estimate and measure of variability reported?* Yes *Power calculation performed at study design?* No *All patients accounted for?* No, the 61 patients who underwent non-standard alloBMT were excluded *Analysis performed on ITT basis?* Not stated			

Reference and Design	Intervention	Patients	Outcome measures
Ohnishi *et al.*, 2000[11] *Date of recruitment*: May 1991 to Dec 1994 *Country* Japan *Study design*: Prospective non-randomised comparative study	*Intervention:* BMT (HLA matched sibling or donor) *Comparison*: IFN-α + chemotherapy *Previous treatment:* Until BMT patients were given chemotherapy± IFN-α *BMT preconditioning:* HU and/or BU *Comparison dose, timing and route*: IFN-α dose adjusted between 3 and 9 MU/day *Rules for dose escalation:* Dose adjusted to maintain WBC counts *Concurrent treatments:* Not stated	*Total number:* 90 (one non-evaluable) *Intervention:* 23 (HLA-identical relative donor 15, HLA-matched unrelated donor 8) *Comparison:* 66 *Disease point:* Chronic phase (unrelated donor group had 88% in chronic phase and 12% in blast phase at time of transplant) *Time since diagnosis:* Time from onset to treatment IFN-α group <6 months 61%, BMT group 23%. Median duration from registration to transplantation in BMT group was 9 months (range 2 to 27) in family donor BMT and 29 months (range 23 to 57) in unrelated donor BMT. *Inclusion criteria:* Newly diagnosed patients with CML, philadelphia chromosome positive, chronic phase, score 0-2 on the European Cooperative Oncology Group performance status and age 20 to 70. *Exclusion criteria:* Serious disorders in heart, lung, kidney or liver, serious infectious and psychiatric disorders, other neoplasms, hypersensitivity reaction against IFN-α and accelerated and blast patients. Patients older than 45 were not eligible for BMT and were given IFN-α. *Participant characteristics:* <u>IFN-α</u> mean age 50 years , male:female ratio 25:41, performance status (ECOG) 0=51%, 1=5%, 2=4% <u>BMT</u> mean age 33 years, male:female ratio 9:14, performance status (ECOG) 0=17%, 1=2% and 2=0%.	*Outcome measures used:* HR, CR, duration of chronic phase and survival *Length of follow-up:* Median follow-up of 54 months (range 30-76) in the IFN-α group
Results In the IFN-α group 47/66 (71%) had a complete HR and in the BMT group (17/23) 74%. In the IFN-α group a complete CR was noted in 5/66 (8%). In the INF-α group the predicted 6-year overall survival rate was 54.5%. In the BMT group the predicted 6-year survival was 93.3% for HLA-identical family donors (one death from GVHD) and the predicted 5.5-year survival is 21.9% for unrelated donors (3 deaths from GVHD). When survival was assessed post transplantation the predicted 5-year survival for family donor BMT was 93.3% and the predicted 3-year survival for unrelated donor BMT was 29.2%. The outcome of family-donor BMT was excellent compared with patients who achieved a CR. However, the outcome of unrelated-donor BMT was inferior to that of patients with CR.			
Methodological comments *Proper randomisation?* No *Allocation concealment?* Not applicable *Groups similar at baseline?* No, patients were younger in the BMT group due to the exclusion of patients older than 45 years. *Eligibility criteria stated?* Yes *Outcome assessors blinded?* No, some outcomes are objective *Providers of care blinded?* Not possible *Patients blinded?* Not possible *Point estimate and measure of variability reported?* No *Power calculation performed at study design?* No *All patients accounted for?* Yes *Analysis performed on ITT basis?* Yes			

Reference and Design	Intervention	Patients	Outcome measures
Ohnishi *et al.*, 2001[12] *Date of recruitment*: Feb 1995 to Nov 1999 *Country* Japan (multicentre) *Study design*: Prospective non-randomised comparative study	*Intervention:* BMT (HLA-identical relative or HLA-matched unrelated donor) *Comparison*: IFN-α *Previous treatment:* Until BMT patients were given chemotherapy± IFN-α *BMT preconditioning:* HU and/or IFN-α *Comparison dose, timing and route*: IFN-α dose adjusted between 3 and 10 MU/day *Rules for dose escalation:* Dose adjusted to maintain WBC counts *Concurrent treatments:* HU for the IFN-α group	*Total number:* 254 evaluable (279 recruited) *Intervention:* Related BMT 50, unrelated BMT 29 *Comparison:* 175 *Disease point:* Chronic phase (For unrelated donors 90% were in chronic phase, 7% accelerated and 3% blast at time of transplant) *Time since diagnosis: M*edian time from registration to transplant 9 months (range 3 to 43) for related donor group and 19 months (range 7 to 45) for unrelated donor group *Inclusion criteria:* Newly diagnosed patients with CML, philadelphia chromosome positive, chronic phase, score 0-2 on the European Cooperative Oncology Group performance status and age 15 plus *Exclusion criteria:* Serious disorders in heart, lung, kidney or liver, serious infectious and psychiatric disorders, other neoplasms, hypersensitivity reaction against IFN-α and accelerated and blast patients. Patients older than 50 were not eligible for BMT and were given IFN-α. *Participant characteristics:* <u>IFN-α</u> median age 54 years (range 19 to 79), male:female ratio 110:65, Sokal score 1.01±0.84 <u>BMT- related donor</u> median age 36 years (range 19 to 53), male:female ratio 33:17, Sokal score 0.76±0.27 <u>BMT- unrelated donor</u> median age 31 years (range 17 to 48), male:female ratio 16:13, Sokal score 0.80±0.40	*Outcome measures used:* HR, CR, duration of chronic phase and survival *Length of follow-up:* Median IFN-α group 38 months (range 9 to 66)

Results

In the IFN-α group 148/175 (89%) had a complete HR compared to 53/79 (78%) in the BMT group. In the IFN-α group a major CR was noted in 62/175 (38%) of patients. In the BMT related donors group 2/50 (5%) had a complete CR as did 1/29 (4%) in the unrelated donors group.

For the IFN-α group predicted 5-year survival was 79%. For the related donors BMT group predicted 5-year survival was 72% and for the unrelated donors BMT group was 67%. When survival was assessed post transplant the predicted 4-year survival rate was 76% for the related donors BMT group and the predicted 3.5 year overall survival rate was 68% for the unrelated donors BMT group.

Methodological comments

Proper randomisation? No
Allocation concealment? Not applicable
Groups similar at baseline? No, the BMT groups were significantly younger than the IFN-α group, the WBC count was significantly lower in the IFN-α group than for BMT, and the Sokal score was significantly higher in the IFN-α group than BMT
Eligibility criteria stated? Yes
Outcome assessors blinded? No, some outcomes are objective
Providers of care blinded? Not possible
Patients blinded? Not possible
Point estimate and measure of variability reported? No
Power calculation performed at study design? No
All patients accounted for? Yes
Analysis performed on ITT basis? Yes

10.7 Interferon alpha compared to hydroxyurea: quality assessment and effectiveness

10.7.1 Summary of the quality of included studies comparing interferon alpha to hydroxyurea

Quality criteria	Benelux, 1998[5]	Broustet, 1991[6]	Hehlmann, 1994[78]	The Italian Cooperative Study Group on CML, 1998[21]
Proper randomisation?	?	✔	✔	?
Allocation concealed?	?	?	?	?
Groups similar at baseline?	✔	✔	✔	X
Eligibility criteria stated?	✔	✔	✔	✔
Outcome assessors blinded?	X	X	X	X
Providers of care blinded?	X	X	X	X
Patients blinded?	X	X	X	X
Point estimates and measures of variability?	✔	X	✔	✔
Power calculation performed at study design?	✔	X	✔	?
All patients accounted for?	✔	✔	✔	✔
Analysis performed on ITT?	✔	X	✔	✔

?= not stated/ uncertain, ✔ =yes, x= no

Internal validity

Sample size

The Benelux Study (1998)[5] randomised 100 people to receive IFN-α and 95 to the control group. Hehlmann and colleagues (1994)[78] randomised 133 people to IFN-α, 194 to HU and 186 to BU. Broustet and colleagues (1991)[6] randomised 30 people to IFN-α and 28 to HU and the Italian Cooperative Study Group (1998)[21] randomised 218 people to IFN-α and 104 to conventional chemotherapy.

The Benelux (1998)[5] and Hehlmann (1994)[78] studies performed power calculations prior to the commencement of the studies to ensure adequate sample sizes. Benelux and colleagues (1998)[5] had power (at least 83 patients in each arm) to detect a 20% improvement from 50% to 70% for a 3-year median freedom from progression period (α=0.05, one-sided, power ß=0.8). Hehlmann and colleagues (1994)[78] calculated that they needed 518 patients (130 IFN-α and 194 HU and 194 BU) to detect a ratio of at least 1.42 in the median survival time in favour of IFN-α (α=0.05, two sided, ß=0.20).

The Italian Cooperative study group (1998)[21] detected a statistically significant difference in median survival between the study groups. There is therefore no possibility of a type 2 error due to inadequate sample size.

The Broustet study[6] did not test statistical significance and did not have sufficient power to detect a statistically significant difference between the two study groups. Using Major CR as the main outcome and assuming a 53% response for IFN-α and a 31% response for HU, at least 39 people would be required per group to have 50% chance of declaring their observed difference as significant (α=0.05, two sided).

Selection bias

Two studies described the methods of randomisation (Broustet 1991[6] and Hehlmann 1994[78]) and the other two studies failed to provide details of randomisation (Benelux 1998[5], The Italian Cooperative Study Group on CML 1998[21]). Broustet and colleagues (1991)[6] reported that randomisation of patients to IFN-α or HU was performed by one centre according to a centralised randomisation list, calibrated every four patients. Hehlmann and colleagues (1994)[78] state that randomisation lists were computed according to Elfron and stratified for participating hospitals. Suitable patients were randomised by phone from a central location.

None of the included studies described concealment of group allocation.

The study groups were similar at baseline in three of the included studies (Benelux 1998,[5] Broustet 1991[6] and Hehlmann 1994[78]). The IFN-α and HU groups were similar at baseline for age ,sex and Sokal score in the Benelux (1998)[5] and Broustet studies(1991).[6] The IFN-α and HU groups were similar for age and Sokal score in the Hehlmann study (1994)[78]. The Italian Cooperative Study Group on CML (1998)[21] failed to provide baseline demographic data for the study groups.

The Italian study[21] is prone to bias due to possible inadequate randomisation and possible incomparability of the two study groups.

Performance bias

The comparison groups for all four studies administered treatment orally whereas the intervention group treatment was administered subcutaneously. Few details of concurrent treatments are provided, so it is uncertain whether concurrent treatments varied between intervention and comparison groups.

Rules for dose escalation varied between IFN-α and HU groups. The dose of HU was usually adjusted to maintain the WBC at a particular level. However, in comparison, IFN-α doses were usually adjusted systematically according to response and adverse effects.

Detection bias

None of the studies reported blinding outcome assessors, providers of care or patients. Each of the studies used an objective outcome measure.

Attrition bias

All four studies accounted for all people that were enrolled (Benelux 1998,[5] Broustet 1991,[6] Hehlmann 1994,[78] The Italian Cooperative Study Group on CML 1998[21]). Only the Broustet study (1991)[6] lost contact with patients (n=2). Three studies stated that they performed analysis on an ITT basis (Benelux 1998,[5] Hehlmann 1994,[78] The Italian Cooperative Study Group on CML 1998[21]).

Patients with CML most frequently discontinue treatment due to adverse effects, disease progression, protocol violations, BMT, or personal choice (See following table).

Reasons for discontinuation of treatment interferon alpha versus hydroxyurea

	Benelux, 1998[5]		Broustet, 1991[6]		Hehlmann, 1994[78]		The Italian Cooperative Study Group on CML, 1998[21]	
	IFN-α (n=85)	HU (n=83)	IFN-α (n=30)	HU (n=28)	IFN-α (n=133)	HU (n=194)	IFN-α (n=218)	HU (n=104)
Acceleration or blast crisis	37	52	1	2	-	-	-	-
Adverse reactions	24	4	6	1	24	1	39	-
Intercurrent other diseases	6	6	-	1	-	-	-	-
BMT	16	7	-	-	20	26	-	-
Refusal/ voluntary withdrawal	1	10	3	1	10	11	-	-
Protocol violations	1	4	1	-	-	15	-	-
Treatment too recent	-	-	1	-	-	-	-	-
Loss of contact with patient	-	-	-	2	-	-	-	-
Therapeutic inefficiency/ resistance	-	-	4	-	55	128	-	-
Disease evolved to acute phase	-	-	-	3	-	-	-	-
Second neoplasia	-	-	-	-	2	1	-	-
Total	**85**	**83**	**16**	**10**	**111**	**182**	**114**	**37**

Informative censoring may also be present. This occurs because of a relationship between reasons for censoring (loss to follow-up, protocol violations, bone marrow transplant or disease progression) and prognosis.

Reporting bias

Three studies reported confidence intervals for survival estimates (Benelux 1998,[5] Hehlmann 1994,[78] The Italian Cooperative Study Group on CML 1998[21]).

External validity

The studies all provided sufficient details to make an assessment of generalisability. All studies described eligibility criteria and exclusion criteria (Benelux 1998,[5] Broustet 1991,[6] Hehlmann 1994,[78] The Italian Cooperative Study Group on CML 1998[21]). Patient characteristics such as age, sex and risk scores were provided by three of the studies.(Benelux 1998,[5] Broustet 1991,[6] Hehlmann 1994[78]).

Patients in the IFN-α versus HU studies had more severe disease than patients in the imatinib trial previously discussed (see section 4.2.2, page 43). Patients presenting in clinical practise may however still have more serious disease than those enrolled in these trials which may effect generalisability.

Outcome assessment was not performed independently or blinded, although outcomes were objective.

10.7.2 Patient characteristics and treatment details from interferon alpha studies

Study characteristic	Benelux, 1998[5]	Broustet, 1991[6]	Hehlmann, 1994[78]	The Italian Cooperative Study Group on CML, 1998[21]
Median haemoglobulin level reported (minimum and maximum)	11.8 g/dl (6.1-15.9)	Not stated	IFN-α 11.8 g/dl (4.2-15.4) HU 11.9 g/dl (6.1-16.3)	Not stated
Splenomegaly	IFN-α 61% HU 65%	Not stated	IFN-α 68.3% HU 72.6%	Not stated
Hepatomegaly	Not stated	Not stated	IFN-α 47.9% HU 46.3%	Not stated
Extramedullary involvement	Not stated	Not stated	IFN-α 9.2% HU 3.7%	Not stated
Median age (minimum and maximum or ±SD)	IFN-α 55.7 (20-88) HU 56.4 (27-84)	IFN-α 55.6 (±10.6) HU 58.6 (±7.1)	IFN-α 47.4 (18-85) HU 46.9 (15-84)	Not stated
Sex ratio M:F (% male)	IFN-α 58:42 (58) HU 53:42 (56)	IFN-α 15:9 (63) HU 16:10 (62)	IFN-α 88:45 (66) HU 98:96 (51)	Not stated
Time since diagnosis	Newly diagnosed	Less than 3 months	Newly diagnosed	Not stated
Sokal score	**IFN-α** Low 29% Int 43% High 28% **HU** Low 30% Int 33% High 37%	**IFN-α** Low 29.2% Int 50% High 20.8% **HU** Low 26.9% Int 46.2% High 26.9%	**IFN-α** Low 27.1% Int 35.3% High 37.6% **HU** Low 29.4% Int 33.5% High 37.1%	Not stated
Previous treatment	None	Leukopheresis	None	None
Interferon drug type	IFN α 2b	IFN α 2b	IFN α 2a or 2b	IFN α
IFN-α dose	3MU 5 days/week sc	4MU daily sc	5MU daily sc	9 MU daily sc
Concomitant drugs	HU	Not stated	Not stated	HU, BU
Median length of follow-up	51 months	Not stated	Not stated	112 months

sc= subcutaneous, IFN-α- interferon alpha, HU= hydroxyurea, BU= busulphan, MU= mega units, int= intermediate, M:F= male to female

10.7.3 Results and survival curves for interferon alpha compared to hydroxyurea

Benelux trial[5] followed patients for a maximum of 7 years. The following figure shows overall survival for the IFN-α and HU (control) groups. At 3 years approximately 70% had survived in the control group compared to almost 80% in the IFN-α group. At 5 years survival was approximately 55% in both groups and at 7 years survival was approximately 32% in the IFN-α group compared to 36% in the control group. Overall the two survival curves were not statistically significantly different (p=0.84) (Figure A).

Figure A. Overall survival, derived from data presented in Benelux *et al.* study[5]

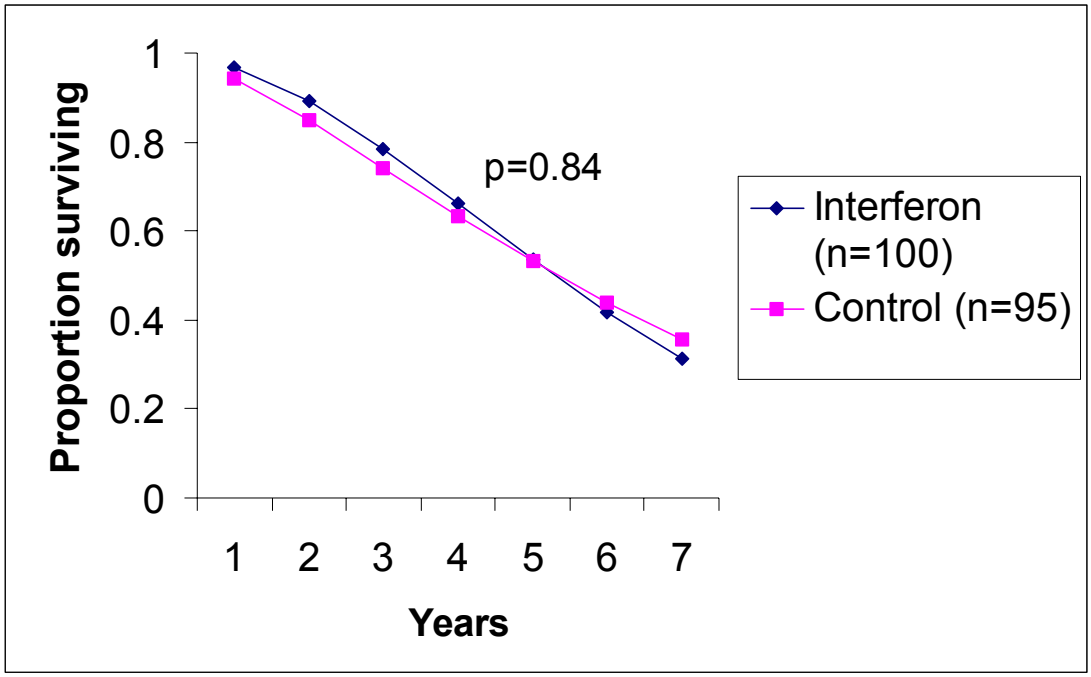
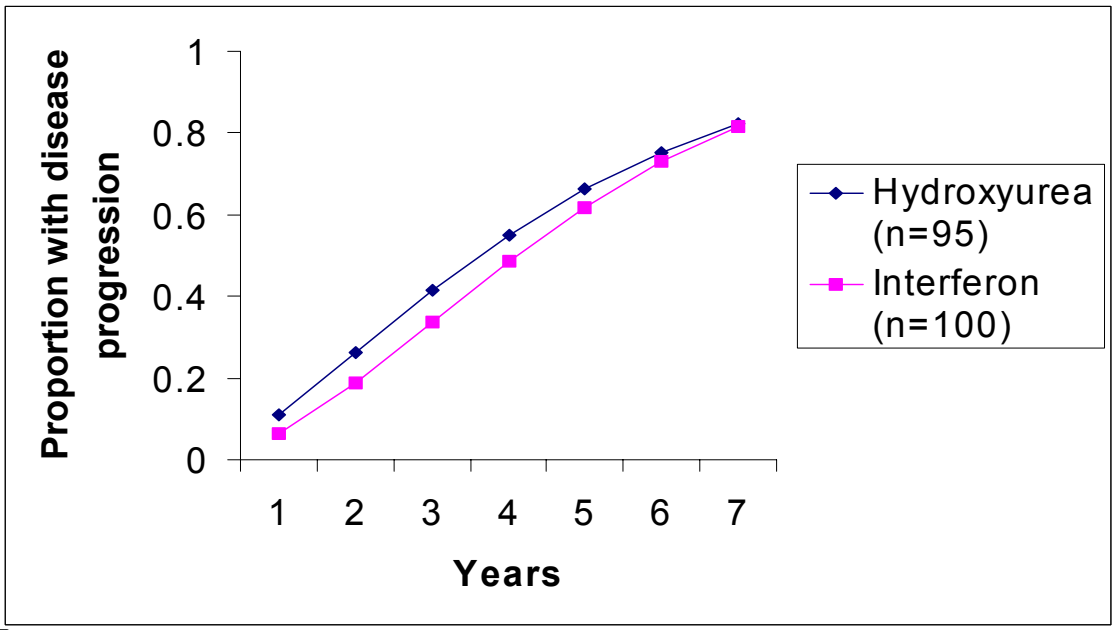


Figure B shows time until disease progression for the IFN-α and HU groups in the Benelux study. At 3 –year follow-up in the Benelux study[5] approximately 40% in the IFN-α group had experienced disease progression compared to approximately 42% in the control group. Follow-up at 5 years showed that approximately 59% in the IFN-α group had progressed compared to approximately 65% in the control group. At 7-year follow-up approximately 85% of the IFN-α group had experienced disease progression compared to 80% in the control group. Overall the time until disease progression curves were not statistically significantly different.

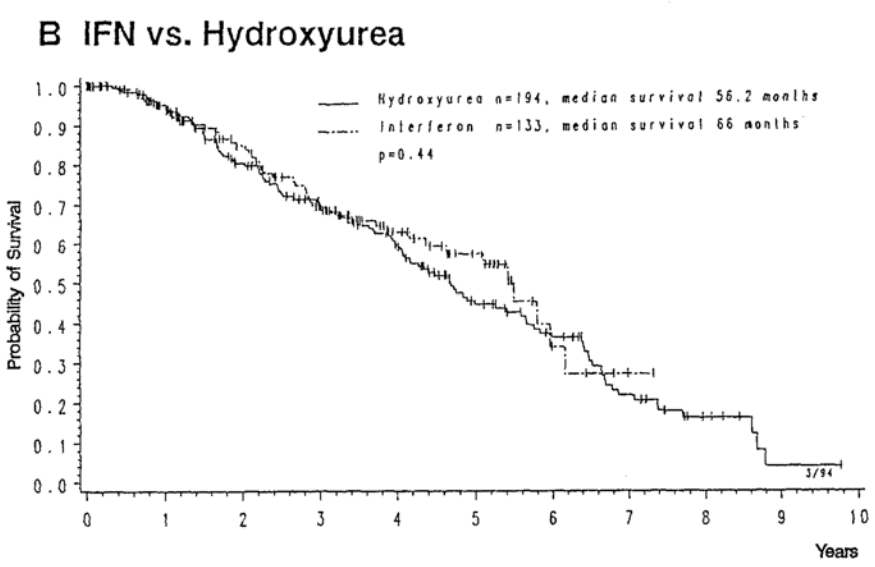
Figure B. Time to disease progression, derived from data presented in the Benelux *et al.* study[5]



The study by Broustet and colleagues[6] does not provide survival curves and time to disease progression curves.

Hehlmann and colleagues[7] present 10 year survival curves of IFN-α compared to HU for treatment of CML (Figure C). Average 3-year survival for both groups was 70%. At 5-year follow-up approximately 58% of the IFN-α group were alive compared to approximately 45% of the HU group. At 7 year follow-up the IFN-α group experienced approximately 28% survival and at 9 year follow-up the HU group experienced approximately 4% survival (the difference in length of follow-up is explained by recruitment of IFN-α patients commencing 2.9 years after recruitment of HU patients).

Figure C. Overall survival, Hehlmann and colleagues[7]



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The Italian Cooperative Study Group on CML[21] followed patients for a maximum of 10 years and compared IFN-α to conventional chemotherapy.

Figure D illustrates overall survival. At 3-year follow-up 74% of the IFN-α group were still alive and 71% of the chemotherapy group. At 5 year follow-up 54% of the IFN-α group had survived compared to 43% of the chemotherapy group. At 10 year follow-up 8% of the IFN-α group were still alive compared to 5% of the chemotherapy group.

Figure D. Overall survival, data derived from Italian Cooperative Study Group on CML study[21]

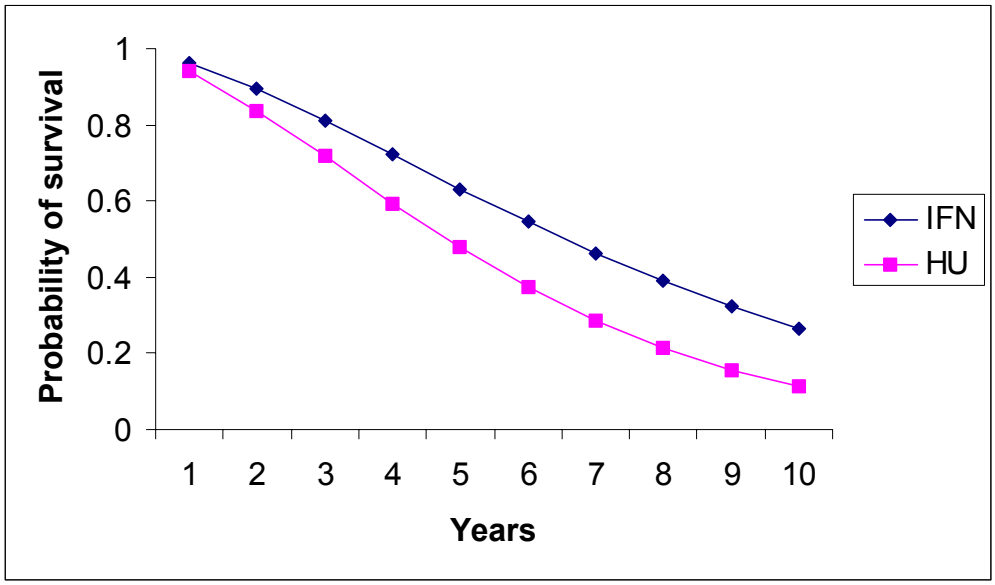
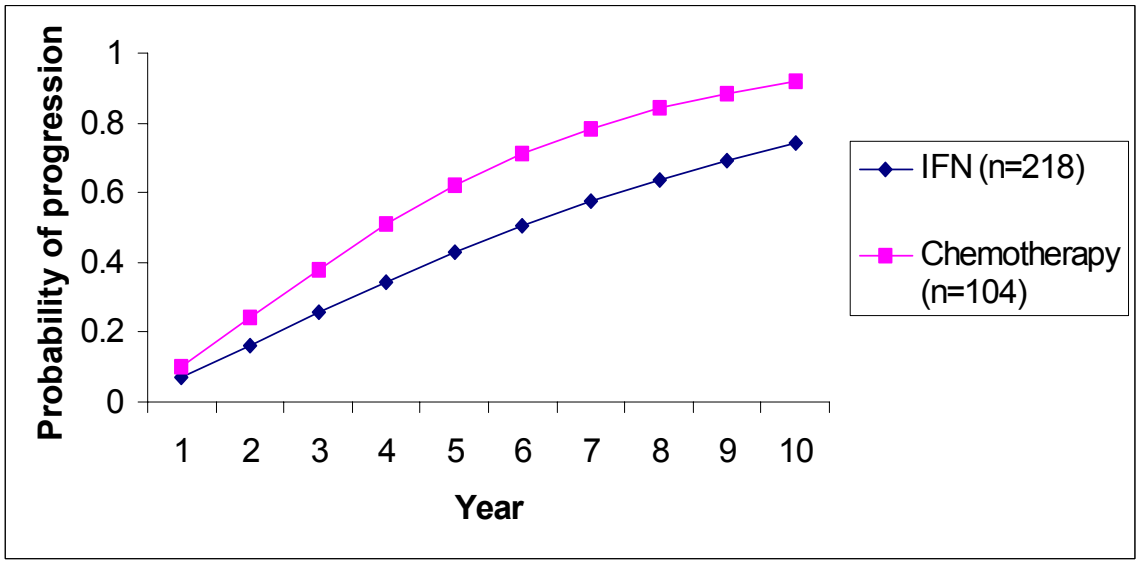


Figure E illustrates the proportion of people progressing over 10 years in the Italian Cooperative Study Group on CML study.[21] At 3 year follow-up approximately 22% of the IFN-α group had experienced disease progression compared to approximately 35% in the chemotherapy group. At 5-year follow-up approximately 43% of the IFN-α group and 60% of the chemotherapy group had progressed. Disease progression was approximately 70% in the IFN-α group and 85% in the chemotherapy group at 10 year follow-up.

Figure E. Disease progression, derived from data presented in Italian Cooperative Study Group on CML[21]



10.7.4 Adverse effects of interferon alpha and hydroxyurea reported in the included studies

Adverse effect	Benelux[5]	Broustet[6]	Hehlmann[78]	The Italian Cooperative Study Group on CML[21]	Benelux[5]	Broustet[6]	Hehlmann[78]	The Italian Cooperative Study Group on CML[21]
	IFN-α				HU			
Fatigue, fever, pain, headache	7%	4.2%	-	11.5%	2.1%	-	0.5%	-
Anorexia, nausea, diarrhoea	-	-	-	6.4%	-	-	-	-
Neurologic, central	-	8.3%	-	2.8%	-	-	-	-
Neurologic, peripheral	-	-	-	2.3%	-	-	-	-
Haematologic	-	-	-	2.8%	-	-	-	-
Skin, itching, alopecia	3%	4.2%	-	3.2%	-	-	-	-
Liver	-	-	-	0.9%	-	-	-	-
Allergic reaction	-	-	-	0.9%	-	-	-	-
Neuropsychiatric	6%	4.2%	-	-	-	-	-	-
Renal including vasculitis	4%%	-	-	-	1.1%	-	-	-
Other	4%	-	-	-	-	-	-	-
Drug eruption	-	-	-	-	1.1%	-	-	-
General intolerance	-	-	-	-	-	11.5%	-	-
Hepatitis	-	8.3%	-	-	-	-	-	-
Thyroid insufficiency	-	8.3%	-	-	-	-	-	-
Inflammatory anaemia	-	4.2%	-	-	-	-	-	-
Flu/neurological/psychiatric/dermatologic	-	-	18%	-	-	-	-	-

10.8 Interferon alpha compared to bone marrow transplant: quality assessment and effectiveness.

10.8.1 Summary of the quality of included studies comparing bone marrow transplant to interferon alpha

Quality criteria	Gaziev, 2002[10]	Ohnishi, 2001[12]	Ohnishi, 2000[11]	Italian Cooperative study Group on CML, 1999[79]	Gale, 1998[9]
Adequate randomisation?	X	X	X	X	X
Allocation concealed?	NA	NA	NA	NA	NA
Groups similar at baseline?	X	X	X	X	X
Eligibility criteria stated?	X	✔	✔	✔	✔
Outcome assessors blinded?	X	X	X	X	X
Providers of care blinded?	NP	NP	NP	NP	NP
Patients blinded?	NP	NP	NP	NP	NP
Point estimates and measures of variability?	✔	X	X	✔	✔
Power calculation performed at study design?	X	X	X	X	X
All patients accounted for?	✔	✔	✔	✔	✔
Analysis performed on ITT?	✔	✔	✔	?	NA

?= not stated/ uncertain, ✔ =yes, x= no, NP= not possible, NA= not applicable

Internal validity

Sample size

The sample sizes varied from 66 to 659 in the IFN-α treatment groups and from 23 to 518 in the BMT treatment groups (see following table). None of the studies performed power calculations prior to the commencement of their studies. It is possible that some studies did not have sufficient power to detect a difference between the study groups.

Numbers of included patients in each study arm and breakdown of types of BMT

	IFN-α	HLA identical sibling donors	Identical twins	HLA identical relative donor	Unrelated donor	Total BMT
Gaziev *et al.*, 2002[10]	70	102	2	1	0	105
Ohnishi *et al.*, 2001[12]	175	0	0	50	29	79
Ohnishi *et al.*, 2000[11]	66	23	0	0	0	23
Italian Cooperative Study Group on CML, 1999[79]	659	153	1	9	18	181
Gale *et al.*, 1998[9]	196	518	0	0	0	518

Selection bias

None of the studies randomised people to study groups and it is questionable whether randomisation between these two possible treatments would be ethical. The studies by Ohnishi and colleagues (2001 and 2000)[11;12] enrolled people prospectively, and both study

groups were enrolled at the same time. The other studies[9;10;79] appear to be retrospective comparisons of series of patients in available databases. Some of the series used for comparison originally enrolled patients consecutively.

None of the studies concealed treatment allocation, however it is unlikely that allocation concealment would be possible with the current comparison between bone marrow transplant and a drug therapy.

None of the studies had similar baseline characteristics for the two groups. This is due to the different management of patients according to age. Older patients are not generally considered suitable for BMT so in all studies the BMT group is significantly younger than the IFN-α group. Although this is understandable in clinical practice it does leave each of the studies prone to selection bias and difficulty in interpreting results and comparing therapies.

Performance bias

There are systematic differences in how patients undergoing IFN-α therapy and BMT are treated apart from the actual intervention itself. BMT requires intensive preconditioning with chemotherapy, requires an inpatient stay and requires different concurrent therapies when compared to IFN-α treatment alone.

These systematic differences in care other than the intervention under investigation may affect the outcomes of the study and lead to performance bias.

Detection bias

None of the studies reported blinding outcome assessors. Outcomes such as death, cytogenetic response and haematological response are however, objective so that blinding of outcome measurement becomes less important. In circumstances such as this where one treatment (BMT) is very invasive and a major procedure and the other is a drug therapy (IFN-α), it is not possible to blind providers of care or patients themselves to treatment allocation.

Attrition bias

All of the included studies accounted for all patients, although one study excluded 61 of the patients enrolled who underwent non-standard BMT from the analysis. [79]

Three studies stated that they performed analysis on an intention-to-treat basis,[10-12] one did not report any loss to follow-up[9] and the other study did not comment.[79]

None of the included studies reported the specific reasons, or the numbers associated with each reason for patients dropping out. The only information available is the number who died based on the survival curves (see below).

Reporting bias

Three studies report point estimates as well as measures of variability (confidence intervals for survival estimates).[9;10;79]

External validity

The included studies provided information on which to make assessments regarding generalisability. Four studies provided details of exclusion criteria.[9;11;12;79] All studies described the included patients with details of age, gender and risk score.

Outcome assessment was not performed independently or blinded, although outcomes were objective.

10.8.2 Patient characteristics of included studies comparing bone marrow transplant and interferon alpha

Study	Gaziev *et al.*, 2002[10]		Ohnishi *et al.*, 2001[12]		Ohnishi *et al.*, 2000[11]		Italian Cooperative, 1999[79]		Gale *et al.*, 1998 [9]	
Study characteristic	**BMT**	**IFN-α**	**BMT**	**IFN-α**	**BMT**	**IFN-α**	**BMT**	**IFN-α**	**BMT**	**IFN-α**
CML phase	Chronic 84% Accelerated 10% Blast Crisis 6%		*Related donors* Chronic 100% *Unrelated donors* Chronic 90% Accelerated 7% and Blast 3%	Chronic	*Related donor* Chronic 100% *Unrelated donor* Chronic 88% Blast 12%	Chronic	120 people in standard alloBMT group were all in chronic phase	Unable to ascertain	Chronic	Chronic-
Median haemoglobulin level reported	-	-	-	-	-	-	11.7±1.9g/dL g/L	*IFN-α* 11.9±2g/dL *Chemo* 12.1±2.0 g/dL	12 (2-17) g/dl	12 (4-16) g/dl
Median spleen size (cm)	5 (0-16)	5 (0-18)	≥10cm *Related donor* 19% *Unrelated donor* 25%	≥10cm 10%	-	-	7.4±6.9	*IFN-α* 6.4±6.5 *Chemo* 6.5±6.5	3 (0-26)	5 (0-30)
Median age (years)	31 (10-53)	43 (14-55)	*Related donor* 36 (19-53) *Unrelated donor* 31 (17-48)	54 (19-79)	33	50	32	*IFN-α* 41.5 *Chemo* 42	35 (15-54)	41 (15-55)
Sex ratio of male:female (% male)	38:50 (43)	45:25 (64)	*Related donor* 33:17 (66) *Unrelated donor* 16:13 (55)	110:65 (63)	9:14 (23)	25:41 (38)	71:49 (59)	*IFN-α* 190:132 (59) *Chemo* 192:145 (57)	331:217 (60)	119:77 (61)

Study	Gaziev *et al.*, 2002[10]		Ohnishi *et al.*, 2001[12]		Ohnishi *et al.*, 2000[11]		Italian Cooperative, 1999[79]		Gale *et al.*, 1998 [9]	
Time since diagnosis (months)	-	-	*Related donor* 9 (3-43) *Unrelated donor* 19 (7-45)	Newly diagnosed	*Related donor* 9 (2-27) *Unrelated donor* 29 (23-57)	Newly diagnosed	15.1±10.4	Previously untreated	10.1 (2-84)	Newly diagnosed
Sokal score	Low 59%, Int 32%, High 9%	Low 68%, Int 29%, High 3%	Mean *Related donor* 0.76±0.27 *Unrelated donor* 0.80±0.40	Mean 1.01±0.84	-	-	Low 49%, Int 29%, High 22%	*IFN-α* Low 50%, Int 27%, High 23% *Chemo* Low 45%, Int 32%, High 19%	Low 41%, Int 37%, high 22%	Low 37%, Int 42%, High 21%

10.8.3 Treatment details of included studies comparing bone marrow transplant and interferon alpha

Four of the five included studies stated that people received chemotherapy and/or IFN-α prior to receiving a BMT. Three of the five included studies stated the concurrent treatments that people undergoing BMT received. The dose of IFN-α therapy was stated by three studies and ranged from 3 to 9MU/day. The other two studies stated that doses varied mainly in order to maintain a certain WBC count.

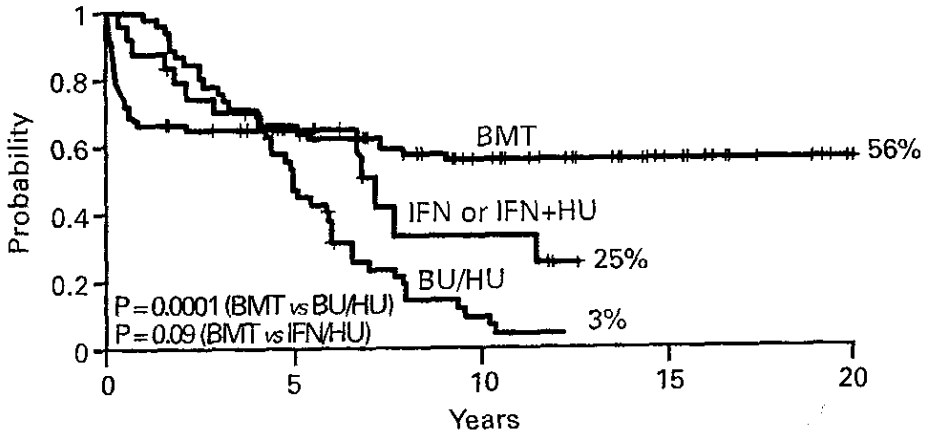
Study	Gaziev *et al.*, 2002[10]	Ohnishi *et al.*, 2001[12]	Ohnishi *et al.*, 2000[11]	Italian Cooperative, 1999[79]	Gale *et al.*, 1998[9]
Previous treatment for BMT group	BU	Chemo±IFN-α	Chemo±IFN-α	IFN-α or HU	IFN-α ± HU
Type of drug treatment	IFN-α	IFN-α	IFN-α2b	IFN-α	Interferon
IFN-α dose	Varying	Adjusted to maintain WBC	3-9MU/day	9MU/day	5MU/day
Type of BMT	HLA-identical sibling 102, identical twin 2, HLA-identical relative 1	HLA-identical relative 50, HLA-matched unrelated 29	HLA-identical relative 15, HLA-matched unrelated 8	HLA-identical sibling 153, identical twin 1, partially-HLA matched relative 9, HLA matched unrelated donor 18	HLA-identical sibling donor
Concurrent treatments for BMT	Prophylactic antibiotics, acyclovir, amphotericin B and trimethoprim/sulfamethoxazole	Not stated	Not stated	Cyclosporine and/or methotrexate	Post transplant methotrexate, cyclosporine
Median length of follow-up IFN-α group (months)	46.8 (12-144)	38 (9-66)	54 (30-76)	Not stated	78
Median length of follow-up BMT group (months)	Not stated	Not stated	Not stated	Not stated	51.6

sc= subcutaneous, IFN-α= interferon alpha, BMT= bone marrow transplant, MU= mega units, int= intermediate, M:F= male to female

10.8.4 Results for interferon alpha compared to hydroxyurea and survival curves

The overall survival curve for IFN-α compared to bone marrow transplant from the Gaziev study[10] is shown in the Figure F. It can be seen that people receiving IFN-α had better survival during the first four years compared to BMT. After four years the survival advantage switches to BMT and the difference increases as time progresses.

Figure F. Overall survival, Gaziev and colleagues[10]



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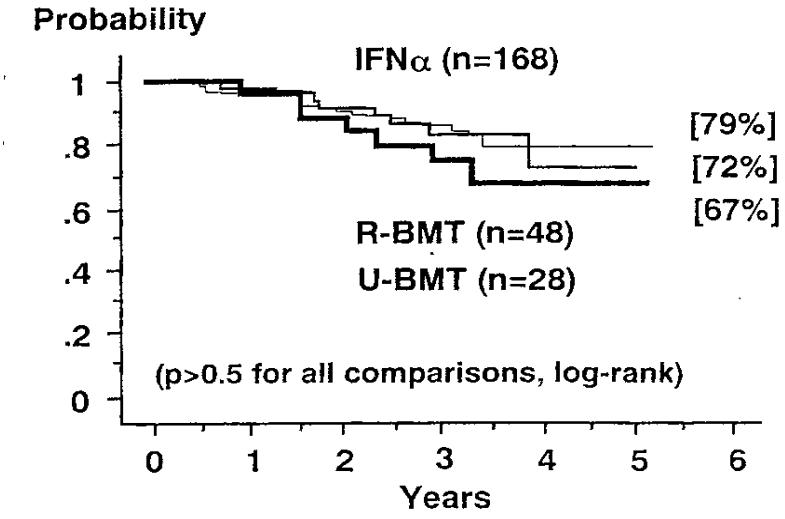
Ohnishi and colleagues in their later study[12] report the probability of survival associated with related donor BMT (R-BMT), unrelated donor BMT (U-BMT) and IFN-α alpha over 5 years (Figure G). There is no statistically significant survival difference between the three groups.

Figure G. Overall probability of survival, Ohnishi and colleagues[12]



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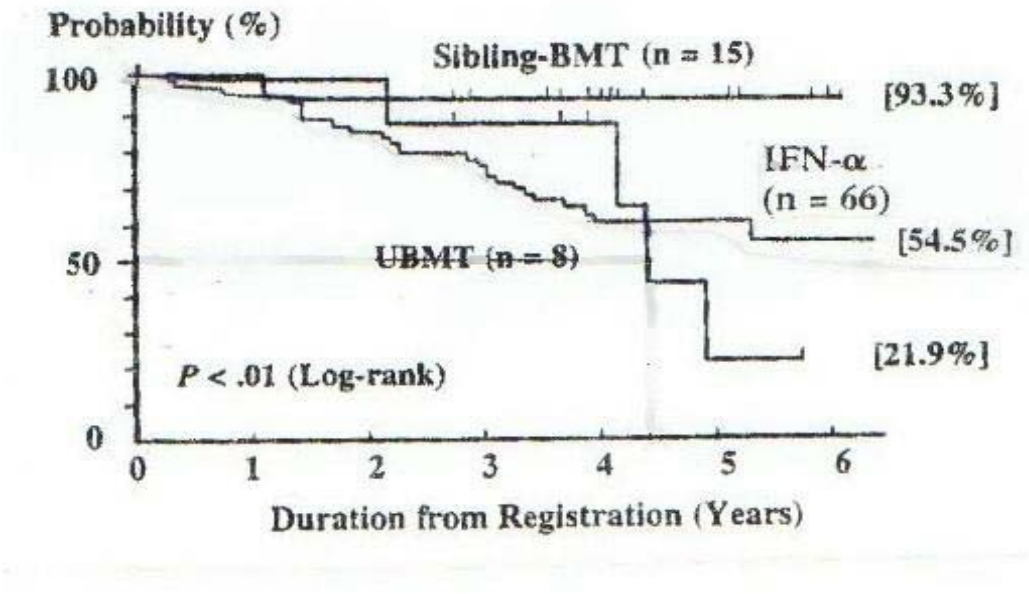
Ohnishi and colleagues (2000)[11] present curves for treatment with IFN-α and sibling donor or unrelated donor BMT with follow-up to a maximum of 6-years (Figure H). Interestingly when comparing treatments in this study IFN-α does not have an initial survival advantage. Sibling donor BMT is associated with higher survival than unrelated donor BMT and treatment with IFN-α. Unrelated donor BMT has a survival advantage over IFN-α up until the curves would cross at approximately 4.3 years.

Figure H. Probability of survival for those treated with interferon alpha or bone marrow transplant, Ohnishi *et al.*, 2000[11]



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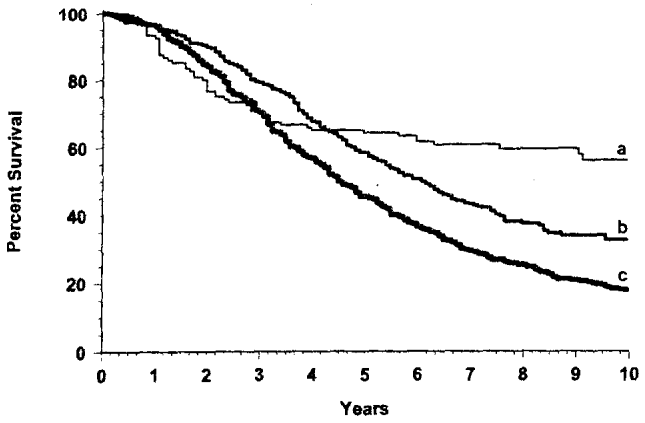
The Italian Cooperative Study Group on CML[79] presents an overall survival curve with a maximum of 10 years follow-up data comparing bone marrow transplantation (a), IFN-α therapy (b) and conventional chemotherapy (HU/BU) (c) (Figure I). Both drug therapies have a survival advantage over BMT in the initial few years after treatment. Bone marrow transplant is associated with better survival than conventional chemotherapy (HU/BU) after approximately 3 years and better survival than IFN-α after 4.5 years.

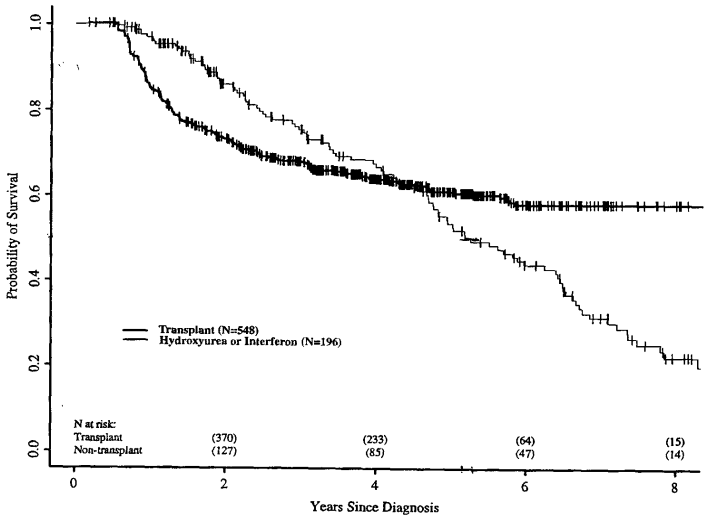
Figure I. Overall survival for bone marrow transplant compared to interferon alpha and chemotherapy (HU/BU), derived from data presented in the Italian Cooperative Study Group on CML[79]



a) bone marrow transplant, b) interferon alpha, c) conventional chemotherapy (HU/BU)

Gale and colleagues[9] compared persons receiving HLA-identical sibling donor bone marrow transplants with drug treatment (HU or IFN-α) for a maximum period of 8 years (Figure J). There is a survival advantage for persons receiving drug therapy until 4.5 years.

Figure J. Overall survival, derived from data presented by Gale and colleagues[9]



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10.8.5 Complications of BMT reported in the included studies

Study	Italian Cooperative Study, 1999[79]	Ohnishi *et al.*, 2000[11]	Gaziev *et al.*, 2002[10]
Complications	**BMT**	**BMT**	**BMT**

Death due to transplant related complications	43/120 (36%)	-	47/105 (45%)
Death due to GVHD	-	Related donors 1/15 (7%) Unrelated donors 3/8 (38%)	-
Death due to thrombocytopenic purpura	-	Unrelated donors 1/8 (13%)	-
Rejection or graft failure	-	-	0
GVHD* (grade II-IV)	-	-	38/100 (38%)
GVHD* (grade III-IV)	-	-	23/100 (23%)
Fungal infections	-	-	33/100 (33%)
Candida species infections	-	-	24/100 (24%)
Cytomegalovirus infection	-	-	13/100 (13%)
Relapse	15/120 (13%)	-	16/105 (15%)

The authors and organisations listed are all those registered as participating in the trial. It is reported that both these trials have been halted because of poor recruitment following the advent of imatinib (Prof J Apperley, Hammersmith Hospital London, personal communication 2003).

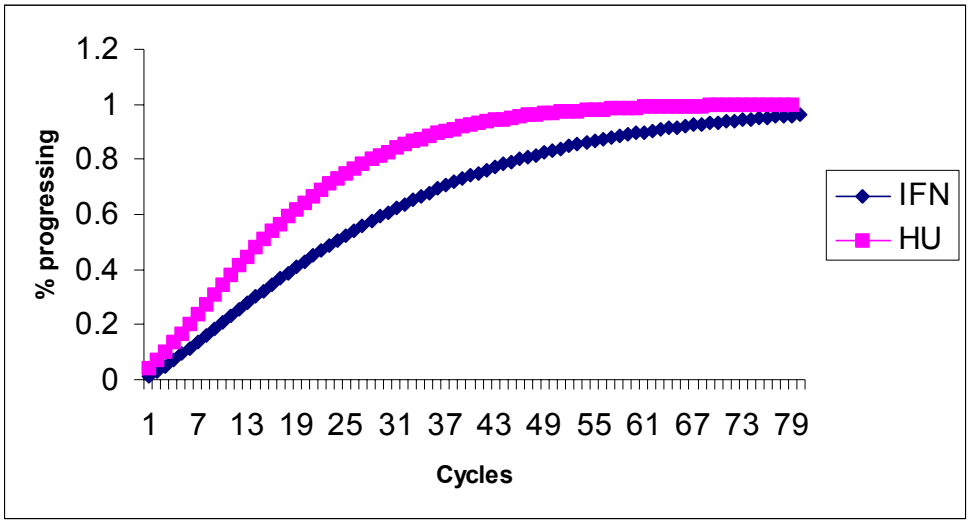
10.8.6 Studies of bone marrow transplant and interferon alpha studies currently in progress

Study/ question	Principal investigator(s)	Organisation	Expected completion date	Study Design	Patients	Methodology
An MRC/ECOG prospective randomised study to compare interferon-a nl (Wellferon) vs 'IdAC' chemotherapy and autografting followed by Wellferon in patients with newly diagnosed chronic phase chronic myeloid leukaemia (CML2000) (CML IV)	Goldman J O'Brien S Rowe J Tallman M	Hammersmith Hospital London Victoria Royal Infirmary, Newcastle, UK Rush-Presbyterian-St Luke's Medical Center, Chicago, USA NWU, Chicago, USA (multicentre)	Closed	RCT	Newly diagnosed chronic phase CML	Multi-centre prospective RCT
CML 2000 (CML Iva) - An MRC Prospective, Randomised Study to Compare Interferon alpha (IFN) +/- Ara-C Against Autografting followed by Interferon alpha +/- Ara-C in Patients with Newly Diagnosed Chronic Phase Chronic Myeloid Leukaemia (CML)	O'Brien S Carella A Reiffers J Apperley J Goldman J	Victoria Royal Infirmary, Newcastle, UK Ospedale San Martino, Genova, Italy. Hôpital du Haut Leveque, Pessac Bordeux Hammersmith Hospital, London Hammersmith Hospital, London (multicentre)	Closed	RCT	Chronic phase CML	Prospective multicentre randomised study

10.9 Validation of survival progression and response curves from model with published literature

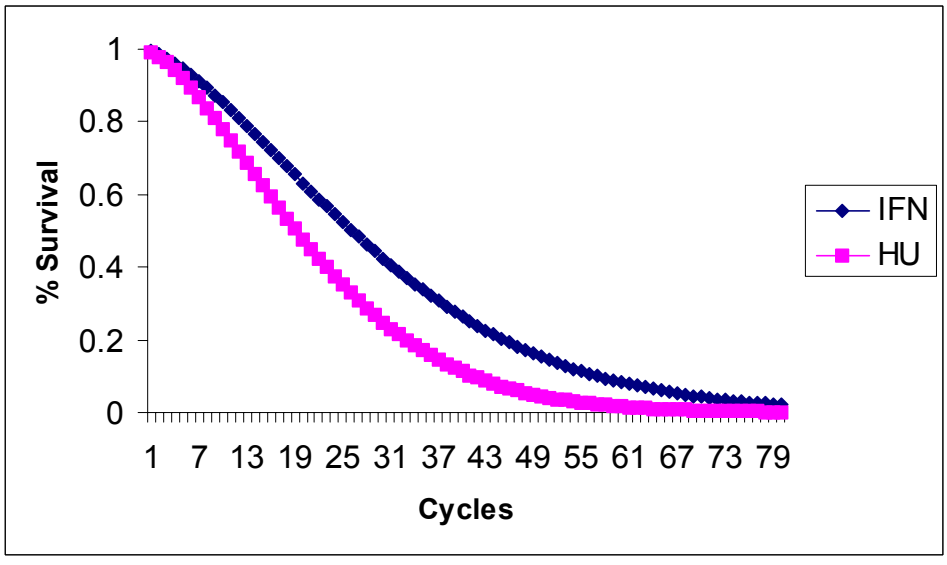
The following figure shows the data used in the economic model for progression which was derived from the Italian Cooperative Study Group[21] using a Weibull distribution. These data are similar to that produced in the original study as seen in Figure D in Appendix 10.7.3 (page 112).

Data for progression used in economic model, derived from Italian study[21] using a Weibull distribution



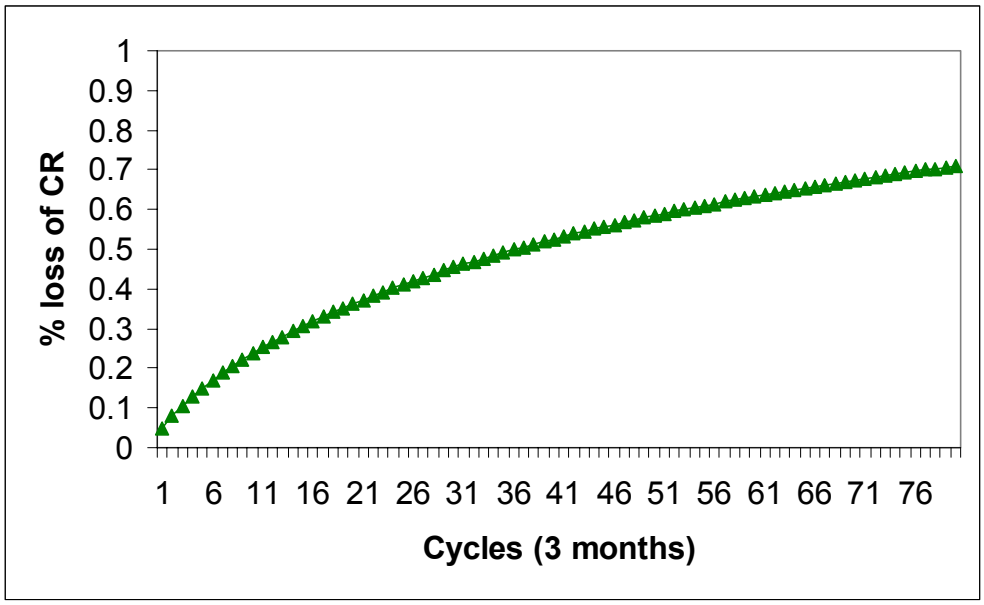
The following figure shows overall survival data used in the economic model. This was derived from the Italian Cooperative Study Group on CML using a Weibull distribution. This data is similar to that shown in the original Italian study report, Figure E in Appendix 10.7.3 (page 112).

Data for survival used in economic model, derived from Italian study[21] using a Weibull distribution

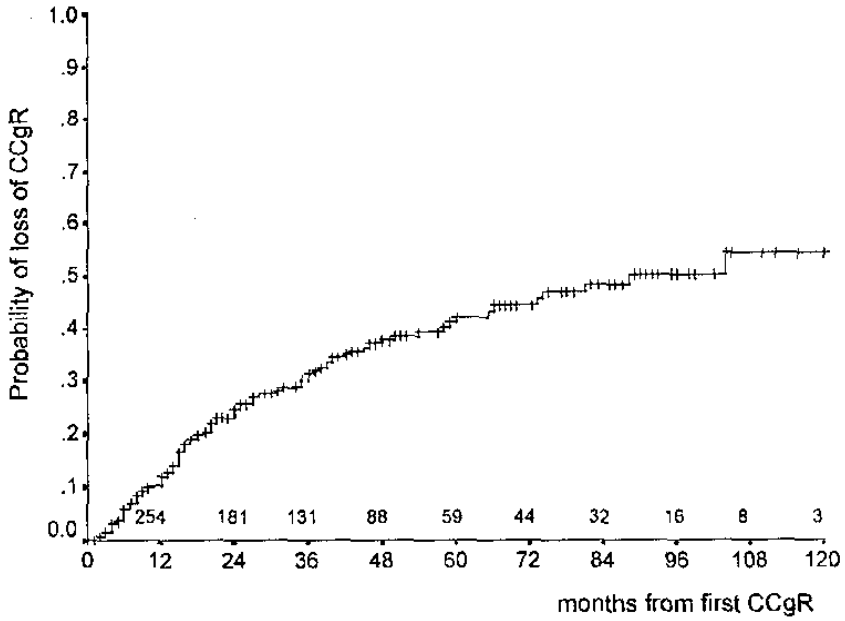


The data for loss of CR was obtained from the study by Bonifazi[25] by fitting a Weibull distribution and is shown in the following figure. The loss of response rate is similar to the original response curve from the Bonifazi study[25] shown as follows.

Percentage loss of response curve from Bonifazi study[25], fitted using a Weibull distribution



Percentage loss of response curve, Bonifazi[25]



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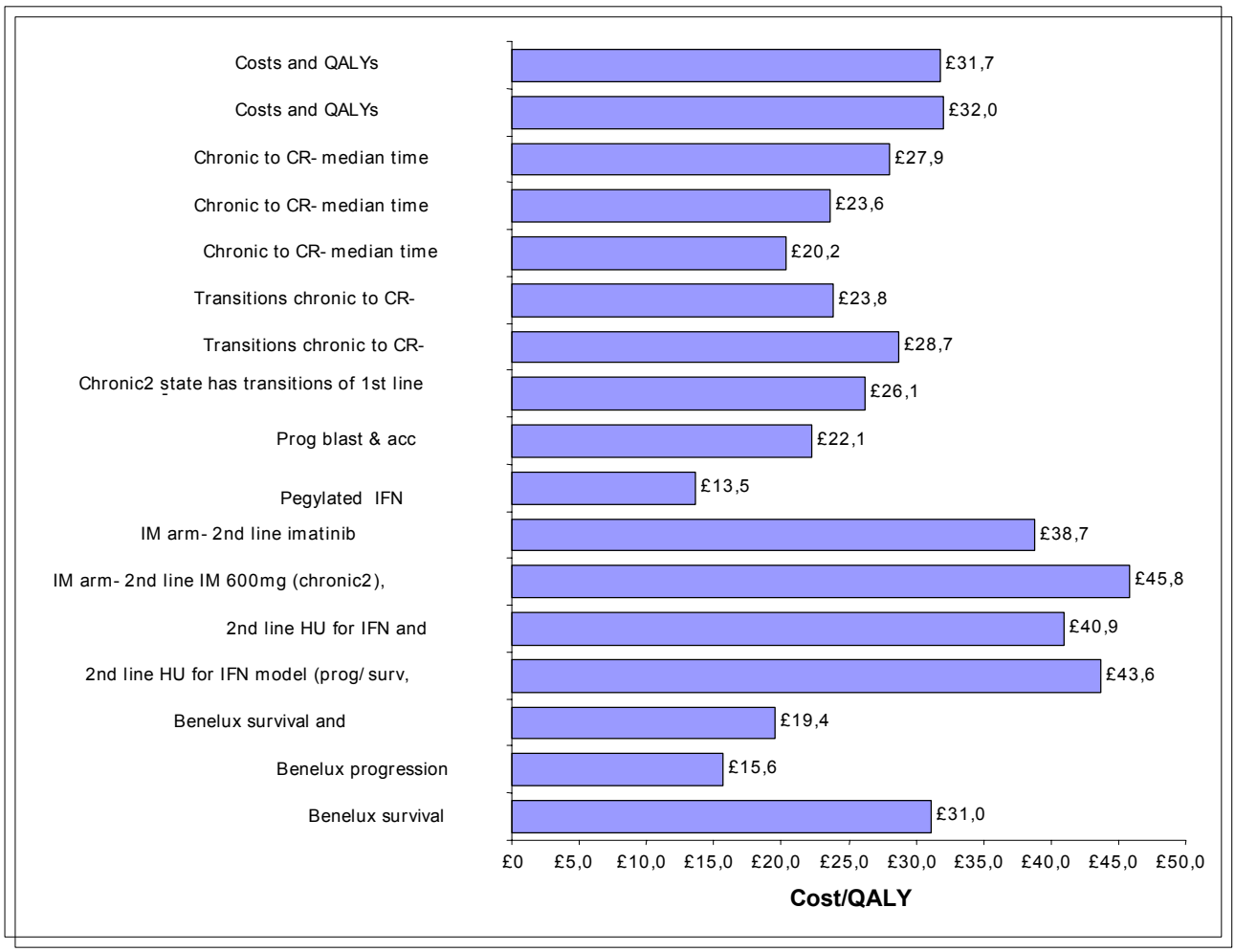
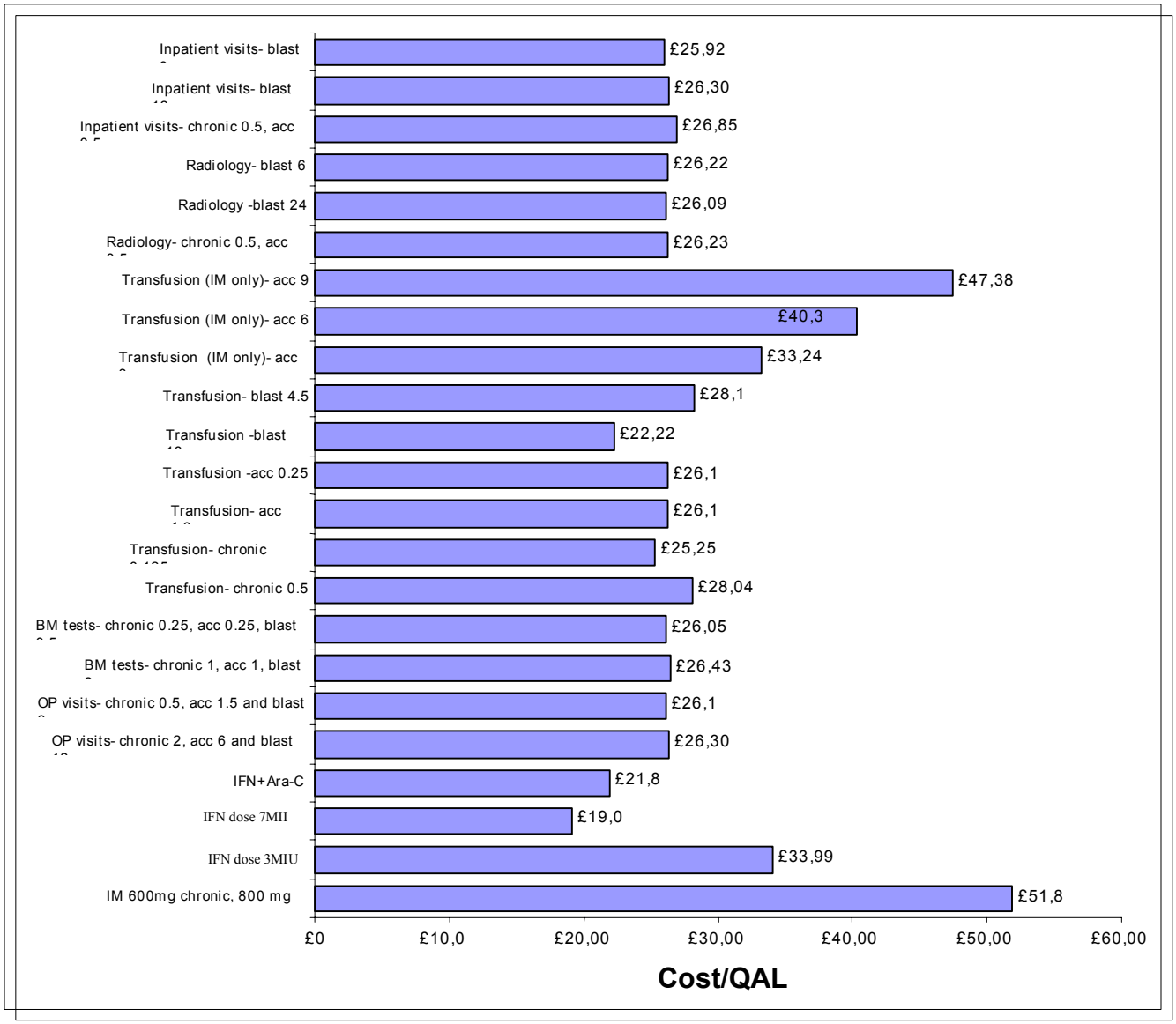
10.10 Sensitivity analysis for independent economic model

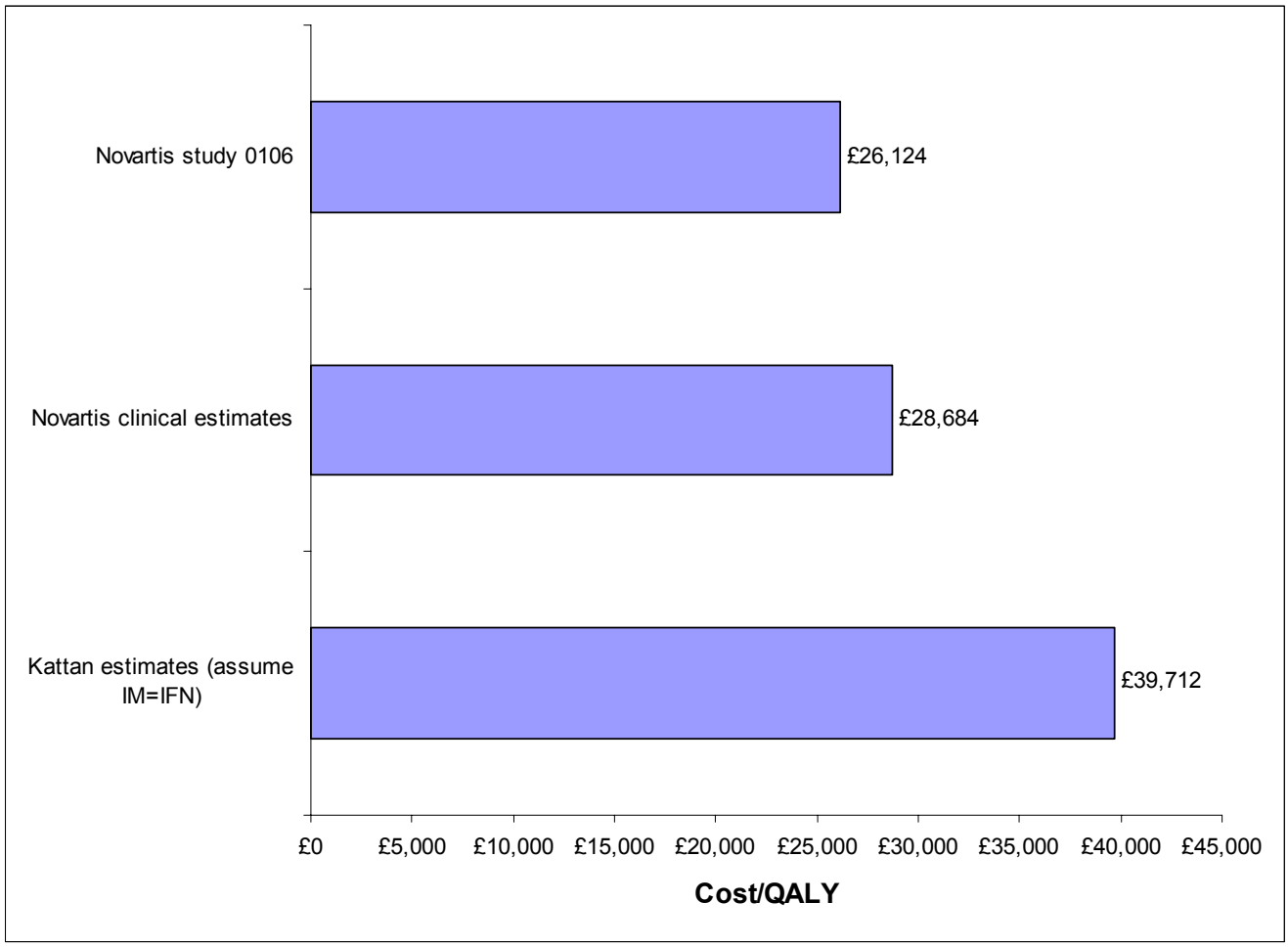
Sensitivity analysis of general model assumptions imatinib versus interferon alpha



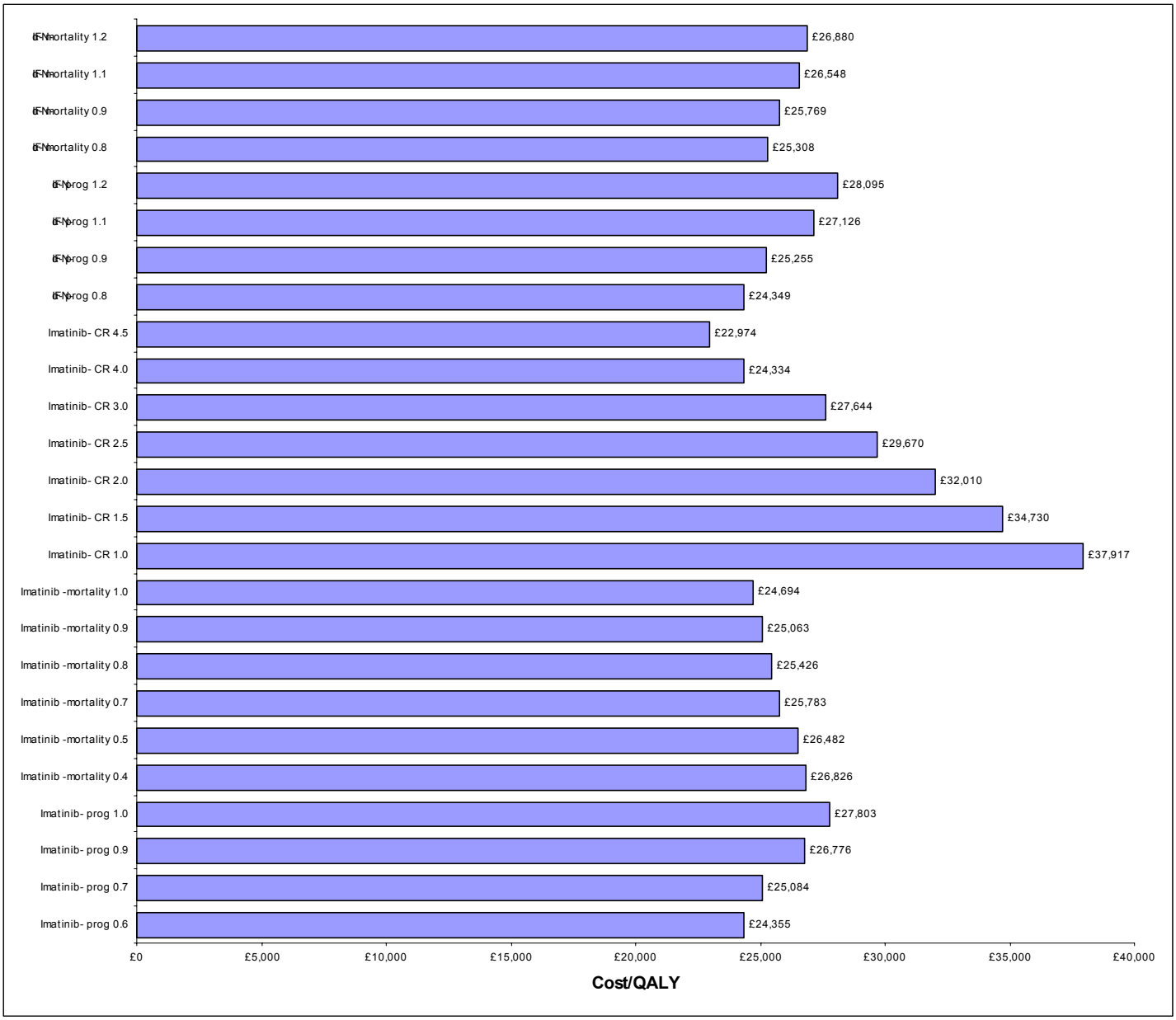
Sensitivity analysis, cost assumptions imatinib versus interferon alpha



Sensitivity analysis, utilities imatinib versus interferon alpha



Sensitivity analysis, relative risks for progression and survival imatinib versus interferon alpha



10.11 Quality assessment of industry economic evaluation

1. Structure	
Is there a clear statement of the decision problem, the context and the perspective?	The model aims to compare the cost-effectiveness of imatinib with interferon-alpha plus ara-C for the treatment of newly diagnoses patients with chronic myeloid leukaemia in whom BMT was not considered a therapeutic option. The structure of the model is consistent with the stated disease problem. The perspective is the NHS which is appropriate.
Is a theory of the underlying disease detailed?	Details of CML and available treatments is presented. The model is consistent with the theory of disease.
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	**Assumptions** -once patients fail treatment with imatinib they receive IFN-α plus ara-C (justified) -once patients patient fail treatment with IFN-α plus ara-C they receive imatinib (justified) -Survival rates after 2 years are based solely on CCR prior to 2 years (lack of long term data makes this hard to verify). -Conditional on CCR status at 2 years, the survival distributions of imatinib and IFN-α are identical (there is no long term data available to verify this) -Progression free survival for Imatinib patients is the same as IFN-α patients after 12 months (lack of data makes this difficult to verify although this is likely to bias against imatinib) -The rate of progression to accelerated and blast phases is the same from chronic, CHR, PHR and CCR states (unlikely to be true, progression slower from CCR state, biased against imatinib as produces more CCR) -there is a constant rate of HR, CR and loss of response applied over the model (these rates will more likely be time dependent) -Patients may only progress to death from causes other than CML, except from blast phase (this is likely to underestimate the death rate as some patients will die from CML causes from the other states) -Movement from first line treatment to second line treatment is assumed to be a constant rate, based on data from 1st 12 months (the rate of progression is unlikely to be constant and will probably increase with time) -Progression free survival on IFN-α 2nd line is assumed to be an average of that for imatinib and HU (no data to support or refute this) -The median duration of palliative care in accelerated phase is 6 months (median survival in accelerated phase, this is probably an underestimate, not explored in sensitivity analysis) -The median duration of palliative care in blast phase is 4.5 months -The cost of adverse events are not considered. (likely to be a conservative estimate as more adverse effects reported with IFN in 106 trial) The implications of relaxing some of these assumptions are explored in sensitivity analyses.
2. Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	A Markov model is appropriate for a chronic condition such as CML.
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	A detailed justification is not provided, although the states do accord with the theory of disease process. Surrogate outcomes are modelled and their relationship with survival is discussed in more detail in section 2.3.2, page 24.
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	No
Have any important disease states been omitted from the model?	No, but all the complexity of the disease process may not have been fully captured.

	captured.
3. Options	
Is there a clear statement of the options being evaluated?	Yes, the model compares the following: Imatinib (first line), IFN-α+Ara-C (second line), Hydroxyurea (third line) with IFN-α+Ara-C (first line), Imatinib (second line), Hydroxyurea (third line)
Do these appear to cover the range of logical and feasible options?	There are additional options that are being used/ considered in clinical practice, particularly for second line treatment after imatinib fails. Some possible treatments include: increased dose of imatinib, combination therapy of imatinib+IFN-α, pegylated IFN-α. It would have been useful if some of these options had been modelled in sensitivity analyses, although there is a lack of currently available data on these various options. Bone marrow transplant is another whole area of options for a patient with CML. BMT has been excluded from the model although the complexity of this justifies the omission.
4. Time horizon	
Is the time horizon of the analysis stated?	The model runs for a total of 40 years. This is long enough to enable stable cost and effect differences between the treatment groups.
If so, is this justified in terms of the underlying disease and the effect of interventions?	The model length may be longer than required as it is unlikely that CML patients would survive this long.
5. Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated.	Yes, cycles were one month.
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	No detailed justification is provided, although a cycle length of 1 month is appropriate for the disease process.
6. Data identification	
Are the sources of parameter values in the model clearly stated?	Yes
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	A formal value of information analysis was not undertaken to determine optimal data to incorporate.
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE*, DARE,* The Cochrane Library*)?*	There is no indication that a formal search was conducted of all low-cost data sources. It is stated that the data used in this model is the "optimal available data", as the only direct comparative data between imatinib and IFN-α. An independent search has not identified further studies. However, other data is used to populate the model
Are ranges specified for parameters?	Some ranges are provided in the industry submission although they do not seem to be incorporated in the economic model, certainly not in the form of stochastic analysis.
Is there evidence to suggest selective use of data?	The model emphasises outcomes other than survival, and models survival based on cytogenetic response and progression-free survival. However, there is no long-term data available for survival.
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	The following parameter estimate was based on expert opinion- "% of patients receiving IFN-α 2nd line treatment who do not progress". The methods used to obtain the estimate were not described.

Are the claims made about the model results tempered by the limitations of the data?	The discussion clearly states that there are significant challenges associated with the lack of long-term efficacy data.
7. Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	Yes, the model is detailed and it is clear how data have been incorporated within the model.
Has a stochastic analysis been undertaken?	No, uncertainty was explored by use of one-way sensitivity analyses
If so, do the distributions in parameter values reflect second order uncertainty?	Not applicable
Have appropriate distributions been selected for each parameter?	Not applicable
Have interval rates been translated into transition probabilities using the appropriate formula?	Yes a separate sheet titled “calc of trans probs” is provided and contains appropriately translated transition probabilities.
If appropriate, has a half cycle correction been applied to adjust time-relate estimate in the model?	It is not clear whether a half cycle correction has been applied to the model, although it is not likely to have a significant impact on overall estimates.
8. Internal consistency	
Is there a statement about the tests of internal consistency that were undertaken?	The model provides estimates of cost-utility using two different methods of calculating progression-free survival. The resulting ICERs were £18,865 and £26,850. These two methods are reasonably similar.
9. External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	A search of the literature revealed no relevant published cost-effectiveness studies of imatinib and interferon for first line treatment of CML. This is reasonable.
Have any comparisons of the outputs of the model with independent external sources been reported?	The model reports that 18-month data for progression free survival presented at the American Society of Hematology was 96.7%, compared to 93% and 94% modelled estimates using the two different methods. Once again this indicates that the economic model is making conservative estimates.
If so, are the conclusions justified? Have discrepancies been investigated and explained?	Conclusions do appear reasonable and estimates are likely to be conservative.

11 References

1. Sawyers C. Chronic Myeloid Leukemia. *N Engl J Med* 1999;340:1330-40.

2. Hernandez-Boluda JC, Cervantes F, Alvarez A, Costa D, Montserrat E. Single-agent therapy with oral mercaptopurine for nonlymphoid blast crisis of chronic myeloid leukemia. *Ann Hematol* 2001;80:516-20.

3. Talpaz M,Silver RT,Druker B et al.Glivec TM (imatinib meysylate) Induces Durable Hematologic and Cytogenetic Responses in Patients with Accelerated Phase Chronic Myeloid Leukemia: Results of a Phase II Study. *Novartis Pharma AG* 2001;11-9-0001.

4. Kumar P. Clinical Medicine 4th edition. *Clinical Medicine 4th edition* 2001;4:425-32.

5. Benelux-CML-Study-Group-. Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-alpha 2b for chronic myeloid leukemia. The Benelux CML Study Group. *Blood* 1998;91:2713-21.

6. Broustet A, Reiffers J, Marit G, Fiere D, Jaubert J, Reynaud J *et al*. Hydroxyurea versus interferon alfa-2b in chronic myelogenous leukaemia: preliminary results of an open French multicentre randomized study. *European Journal of Cancer* 1991;27 Suppl 4:S18-S21.

7. Hehlmann R, Heimpel H, Hasford J, Kolb HJ , Pralle H, Hossfeld DK *et al*. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood* 1994;84:4064-77.

8. Bolton AE, Gathmann I. A phase III study of STI571 versus Interferon alpha (IFNa) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Bassel Switzerland: Novartis Pharma AG, 2002.

9. Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H *et al*. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. *Blood* 1998;91:1810-9.

10. Gaziev D, Galimberti M, Polchi P, Angelucci E, Giardini C, Baronciani D *et al*. Fate of chronic myeloid leukemia patients treated with allogeneic bone marrow transplantation or chemotherapy and/or interferon at a single center: long-term results. *Bone Marrow Transplant* 2002;29:1-8.

11. Ohnishi K, Minami S, Ueda T, Nishimura M , Tsubaki K, Takemoto Y *et al*. Multicentre prospective study of interferon-alpha and conventional chemotherapy versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia. Kouseisho Leukemia Study Group. *Int J Hematol* 2000;72:229-36.

12. Ohnishi K, Ino T, Kishimoto Y, Usui N, Shimazaki C, Ohtake S *et al*. Multicentre prospective study of interferon-alpha versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: a preliminary analysis. *Cancer Chemother Pharmacol* 2001;48:S59-S64.

13. Taylor PA. Northern Leukaemia Register. *Northern Leukaemia Register* 2000.

14. Lamvik J,Brinich L,Dahl I,Sjo M,Nesthus I,Tangen J et al Chronic myeloid leukemia in health regions 1,3,4 and 5 during the period 1990-96. *Tidsskrift-for-den-Norske-laegeforening* 1999;119:1736.

15. Perkins D,Brennan S,Carstairs K,Bailey D,Pantalony D,Poon A et al. Regional cancer statistics: a report on 1143 diagnostic cases. *Cancer Genet Cytogenet* 1997;96:64-80.

16. Mauro MJ,.Druker BJ. STI571: Targeting BCR-ABL as therapy for CML. *Oncologist* 2001;6:233-8.

17. Clarkson B SA. Linkage of proliferative and maturational abnormalities in chronic myelogenous leukaemia and relevance to treatment. *Leukemia* 1993;7:1683-721.

18. Jahagirdar BN, Miller JS, Shet A, Verfaillie CM. Novel therapies for chronic myelogenous leukemia. *Exp Hematol* 2001;29:543-56.

19. Bose S,Deninger M,Gora-Tybor J,Goldman JM,Melo JV. The presence of typical and atypical bcr abl fusion genes in leukocytes of normal individuals: biological significance and implications for the assessment of minimal residual disease. *Blood* 1998;92:3362.

20. Minot G, Buckman T, Isaacs R. Chronic myelogenous leukemia. *JAMA* 1924;82:1489-94.

21. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Long-term follow-Up of the italian trial of interferon-alpha versus conventional chemotherapy in chronic myeloid leukemia. The Italian The Italian Cooperative Study Group on Chronic Myeloid Leukemia. *Blood* 1998;92:1541-8.

22. Hehlmann R, Heimpel H, Hasford J, Allan N, Burnett A, Shepherd P *et al*. Hydroxyurea versus busulphan for chronic myeloid leukaemia: An individual patient data meta-analysis of three randomized trials..*British Journal of Haematology.2000; 110./3 (573.576.)* 2000;110:573.

23. Giralt S, Kantarjian H, Talpaz M. The natural history of chronic myelogenous leukemia in the interferon era. *Semin Hematol* 1995;32/2:-158.

24. Hasford J, Pfirmann M, Hehlmann R, Allan NC, Baccarani M, Nelemans JC *et al*. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. *J Natl Cancer Inst* 1998;90/11:-858.

25. Bonifazi F,De Vivo A,Rosti G,Guilhot F,Guilhot J,Trabacchi E *et al*. Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. *Blood* 2001;98:3074-81.

26. Hehlmann R, Ansari H, Hasford J, Heimpel H, Hossfeld DK, Kolb HJ *et al*. Comparative analysis of the impact of risk profile and of drug therapy on survival in CML using Sokal's index and a new score. German chronic myeloid leukaemia (CML)-Study Group. *Br J Haematol* 1997;97:76-85.

27. Hehlmann R, Hochhaus A, Berger U, Muth A , Kolb HJ, Pfirrmann M *et al*. Survival after allogenous bone marrow transplantation in patients with chronic myeloid leukemia (CML) is not influenced by pretransplant interferon alpha therapy. *Br J Haematol* 1998;102:317.

28. Bonifazi F, De Vivo A, Rosti G, Tiribelli M, Russo D, Trabacchi E *et al*. Testing Sokal's and the new prognostic score for chronic myeloid leukaemia treated with < alpha >-interferon. *Br J Haematol* 2000;111:587-95.

29. Talpaz M. Interferon-alfa-based treatment of chronic myeloid leukemia and implications of signal transduction inhibition. *Semin Hematol* 2001;38:22-7.

30. Wisloff F HM. Effect of interferon on the health related quality of life of multiple myeloma patients: results of a Nordic randomised trial comparing melphalan-prednisone to melphalan-prednisone plus alpha interferon. *Br J Haematol* 1996;94:324-32.

31. Bertero C, Eriksson BE, Ek A C. Explaining different profiles in quality of life experiences in acute and chronic leukemia. *Cancer Nurs* 1997;20:100-4.

32. Maloisel F, Uettwiller F, Laplace A, Lioure B, Herbrecht R, Mark M *et al*. Emergence of unusual cytogenetic abnormalities under interferon-alpha therapy in patients with chronic myelogenous leukemia. *Cancer Genet Cytogenet* 1999;113/2:-176.

33. Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F *et al*. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. *N Engl J Med* 1997;337:223-9.

34. Thaler J, Hilbe W, Apfelbeck U, Linkesch W, Sill H, Seewann H *et al*. Interferon-alpha-2C and LD ara-C for the treatment of patients with CML: Results of the Austrian multicenter phase II study. *Leuk Res* 1997;21/1:-80.

35. Baccarani M, Rosti G, De Vivo A, Bonifazi F, Russo D, Martinelli G *et al*. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. *Blood* 2002;99:1527-35.

36. European Agency for the Evaluation of Medicinal Products. Committee for Propritey Medicinal Products European Public Assessment Report: Glivec CPMP/2418/01. 2001.

37. O'Dwyer ME, Mauro MJ, Aust S, Kuyl J, Paquette R, Sawyers C *et al*. Ongoing evaluation of the combination of Imatinib mesylate (Glivec TM) with low dose interferon-alpha for the treatment of chronic phase CML. *European Hematology Association (EHA) Annual Meeting* 2002.

38. O'Brien S, G, Vallance S, E, Craddock C, M. Pegintron and STI571 combination evaluation study (PISCES) in chronic phase chronic myeloid leukaemia. *British Society for Haematology* 2002;42nd Annual Scientific Meeting, Brighton, UK, April#15-18,#2002; British Journal of Haematology [print]#117:3-4.

39. Trabacchi E, Bassi S, Saglio G, Rege-Cambrin G, Bonifazi F, De Vivo A *et al*. Pegylated recombinant interferon alpha2b (Pegintron) associated with imatinib mesylate (Glivec) in Ph chronic myeloid leukaemic (CML) in early chronic phase: a phase II study of the ICSG on CML. *European Hematology Association (EHA) Annual Meeting* 2002.

40. Kalidas M, Kantarjian H, Talpaz M. Chronic myelogenous leukemia. *JAMA* 2001;286:895-8.

41. Davies SM, DeFor TE, McGlave PB, Miller JS, Verfaillie CM, Wagner JE *et al*. Equivalent outcomes in patients with chronic myelogenous leukemia after early transplantation of phenotypically matched bone marrow from related or unrelated donors. *American.Journal of Medicine* 2001;110:339-46.

42. Silver RT, Woolf SH, Hehlmann R, Appelbaum FR, Anderson J, Bennett C *et al*. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: Developed for the American Society of Hematology. *Blood* 1999;94:1517-36.

43. Mughal TI,.Goldman JM. Chronic myeloid leukaemia. STI 571 magnifies the therapeutic dilemma. *Eur J Cancer* 2001;37:561-8.

44. Kumar PCM. Clinical Medicine, Fourth Edition. *Clinical Medicine 4th edition* 1998.

45. Powles R, Mehta J, Kulkarni S, Treleaven J, Millar B, Marsden J *et al*. Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: a randomised trial. *Lancet* 200;355:1199-200.

46. Hochhaus A, Reiter A, Saussele S, Reichert A, Emig M, Kaeda J *et al*. Molecular heterogeneity in complete cytogenetic responders after interferon-alpha therapy for chronic myelogenous leukemia: low levels of minimal residual disease are associated with continuing remission. German CML Study Group and the UK MRC CML Study Group. *Blood* 2000;95:62-6.

47. Tcachuk D WCAMeal. Detection of bcr-abl fusion in chronic myeloid leukaemia by in situ hybridization. *Science* 1990;250:559-62.

48. Cross NC. Competitive polymerase chain reaction to estimate the numbers of Bcr-Abl transcripts of chronic myeloid leukemia. *Blood* 1993;82:1929-36.

49. Baron F, Frere P, Fillet G, Beguin Y. Treatment of leukemia relapse after allogeneic hematopoietic stem cell transplantation by donor lymphocyte infusion and STI-571. *Haematologica* 2001;86:993-4.

50. Hehlmann R, Willer A, Heimpel H, Hasford J, Kolb HJ, Pralle H *et al*. Randomized studies with interferon in chronic myelogenous leukemia (CML) and comparative molecular aspects. *Leukemia* 1997;11/SUPPL. 3:-511.

51. Silver RT, Karanas A, Dear KB, Weil M, Brunner K, Haurani F *et al*. Attempted prevention of blast crisis in chronic myeloid leukemia by the use of pulsed doses of cytarabine and lomustine. A Cancer and Leukemia Group B study. *Leuk Lymphoma* 1992;7:63-8.

52. Sawyers CL. Implications of signal transduction inhibition for the treatment of chronic myeloid leukemia. *Seminars in Hematology* 2001;38:S1-S42.

53. Barthe C, Cony-Makhoul P, Melo JV, Mahon JR. Roots of clinical resistance to STI-571 cancer therapy. *Science* 2001;293:2163.

54. Krystal GW. Mechanisms of resistance to imatinib (STI571) and prospects for combination with conventional chemotherapeutic agents. *Drug Resist.Updat.* 2001;4:16-21.

55. Korycka A,.Robak T. The comparision of influence of STI571 used alone or in combination either with 2-chlorodeoxyadenosine or fludarabine on the normal and chronic myelogenous leukemia progenitor cells in vitro. *European Hematology Association (EHA) Annual Meeting* 2002.

56. Druker BJ. STI571 (Gleevec/Glivec, imatinib) versus interferon (IFN) + cytarabine as initial therapy for patients with CML: results of a randomised study. *Americal Society of Clinical Oncology Annual Meeting* 2002;Abstract no.1.

57. Schad M, Toplay J, Zeller W, Fruehauf S. Imatinib in combination with 17-allylamino-17-dexethoxy-geldanamycin (17-AAG) for treatment of chronic myelogenous leukemia. *European Hematology Association (EHA) Annual Meeting* 2002;Abstract no. 1005.

58. Fruehauf S, Toplay J, Schad M, Ho AD, Zeller WJ. Rationale for combination therapy of chronic myelogenous leukemia with imatinib and irradiation or alkylating agents: implicatios for pretransplant conditioning. *International Society for Experimental Hematology Annual Meeting* 2002;Abstract no. 224.

59. Kantarjian HM, Talpaz M, O'Brien S, Smith TL, Giles FJ, Faderl S *et al*. Imatinib mesylate for Philadelphia chromosome-positive, chronic-phase myeloid leukemia after failure of interferon-alpha: follow-up results. *Clin Cancer Res* 2002;8:2177-87.

60. Novartis Pharmaceuticals UK Ltd. Appraisal of Glivec for 1st line treatment of chronic myeloid leukaemia. Novartis Pharma AG . 2003.

61. Shepherd PC, Richards SM, Allan NC. Progress with interferon in CML--results of the MRC UK CML III study. *Bone Marrow Transplant* 1996;17 Suppl 3:S15-S18.

62. Ohnishi K, Tomonaga M, Kamada N, Onozawa K, Kuramoto A, Dohy H *et al*. A long term follow-up of a randomized trial comparing interferon-alpha with busulfan for chronic myelogenous leukemia. *Leuk Res* 1998;22/9:-786.

63. Chronic-Myeloid-Leukemia-Trialists'-Collaborative-Group. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials. *J Natl Cancer Inst* 1997;89:1616-20.

64. O'Brien S, Guilhot F, Larson R, Gathmann I, Baccarani M, Cervantes F *et al*. Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: a decision analysis. *N Engl J Med* 2003;348:994-1004.

65. Clark TJ, Khan KS, Foon R, Pattison H, Bryan S, Gupta JK. Quality of Life instruments in studies of menorrhagia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2002;104:96-104.

66. Etienne G, Cony-Makhoul P, Mahon FX. Imatinib mesylate and gray hair. *N Engl J Med* 2002;347:446.

67. Drummond A, Micallef-Eynaud P, S, Murphy J, Holyoake T, Drummond M *et al*. A spectrum of skin reactions to the tyrosine kinase inhibitor

imatinib mesylate (STI 571). *British Society for Haematology* 2002;42nd Annual Scientific Meeting, Brighton, UK, April#15-18,#2002; British Journal of Haematology [print]#117:17-science.

68. Milojkovic D, Short K, J, [a]. Dose limiting dermatological toxicity secondary to imatinib mesylate (STI-571) in chronic myeloid leukaemia (CML). *British Society for Haematology* 2002;42nd Annual Scientific Meeting, Brighton, UK, April#15-18,#2002; British Journal of Haematology [print]#117:16-7.

69. Ebnoether M, Stentoft J, Ford J, Buhl L, Gratwohl A. Cerebral oedema as a possible complication of treatment with imatinib. *?* 2002;359:1751-2.

70. Barton JC, Jones SC, Lamberth WC, Reymann MT, Scott VC. Cardiac tamponade associated with imatinib mesylate therapy of chronic myelogenous leukemia. *Am J Hematol.* 2002;71:139-40.

71. Vidal D, Puig L, Sureda A, Alomar A. Sti571-induced Stevens-Johnson Syndrome. *Br J Haematol* 2002;119:274-5.

72. Lim DS,.Muir J. Oral Lichenoid Reaction to Imatinib (STI 571, Gleevec). *Dermatology* 2002;205:169-71.

73. Lim D,.Muir J. Lichenoid eruption to STI 571. *Am J Hematol.* 2002;70:179.

74. Esmaeli B, Prieto VG, Butler CE, Kim SK, Ahmadi MA, Kantarjian HM *et al*. Severe periorbital edema secondary to STI571 (Gleevec). *CANCER* 2002;95:881-7.

75. Konstantopoulos K, Papadogianni A, Dimopoulou M, Kourelis C, Meletis J. Pityriasis rosea Associated with Imatinib (STI571, Gleevec). *Dermatology* 2002;205:172-3.

76. Brouard M,.Saurat JH. Cutaneous reactions to STI571. *N Engl J Med* 2001;345:618-9.

77. Ohyashiki K, Kuriyama Y, Nakajima A, Tauchi T, Ito Y, Miyazawa H *et al*. Imatinib mesylate-induced hepato-toxicity in chronic myeloid leukemia demonstrated focal necrosis resembling acute viral hepatitis. *Leukemia* 2002;16:2160-1.

78. Hehlmann R, Heimpel H, Kolb HJ, Heinze B , Hochhaus A, Griesshammer M *et al*. The German CML study, comparison of busulfan vs. hydroxyurea vs. interferon alpha and establishment of prognostic score 1. *Leukemia & Lymphoma* 1993;11 Suppl 1:159-68.

79. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Monitoring treatment and survival in chronic myeloid leukemia. *J Clin Oncol* 1999;17:1858-68.

80. Liberato NL, Quaglini S, Barosi G. Cost-effectiveness of interferon alfa in chronic myelogenous leukemia. *J Clin Oncol* 1997;15:2673-82.

81. Messori A. A cost-effectiveness of interferon in chronic myeloid leukaemia: analysis of four clinical studies. *Ann Oncol* 1998;9:389-96.

82. Gold, M. R. Siegel J. E. Russell L. B. and Weinstein M. C. Cost-Effectiveness in Health and Medicine. Oxford University Press . 1996.

83. Drummond, M. and McGuire A. Economic Evaluation in Health Care. Oxford University Press . 2001.

84. Freund M, Grote-Metke AF, Nowak RF, Otremba BF, Wormann BF, Koch OF *et al*. Combination of Chemotherapy and Interferon Alfa-wb in the Treatment of Chronic Myelogenous Leukemia. *Semin Hematol* 1993;30:11-3.

85. Warren E, Gordois A, Ward, S, and Scuffham P. The clinical and cost effectiveness of Imatinib (Glivec, STI571) for chronic myeloid leukaemia (CML). American Society of Clinical Oncology Meeting 1094. 2002.

86. Kattan MW, Inoue Y, Giles FJ, Talpaz M, Ozer H, Guilhot F *et al*. Cost-effectiveness of interferon-alpha and conventional chemotherapy in chronic myelogenous leukemia. *Ann Intern Med* 1996;125:541-8.

87. Italian Cooperative Study Group on Chronic Myeloid Leukemia and Italian Group for Bone Marrow Transplantation. A prospective comparison of alpha-IFN and conventional chemotherapy in Ph+ chronic myeloid leukemia. Clinical and cytogenetic results at 2 years in 322 patients. *Haematologica* 1992;77:204-14.

88. Ozer H, George SL, Schiffer CA, Rao K, Rao PN, Wurster-Hill DH *et al*. Prolonged subcutaneous administration of recombinant alpha 2b interferon in patients with previously untreated Philadelphia chromosome-positive chronic-phase chronic myelogenous leukemia: effect on remission duration and survival: Cancer and Leukemia Group B study 8583. *Blood* 1993;82:2975-84.

89. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in CML after cytogenetic response to interferon-alpha therapy. *Ann Intern Med* 1995;122:261.

90. Tarumoto T. Characterization of an STI571-resistant, BCR/ABL-positive cell line: A possible mechanism of resistance. 30th Annual Meeting of the International Society for Experimental Hematology, Tokyo, Japan, August 25-28,2001; Experimental Hematology:39.

91. Druker BJ, Talpaz M, Resta D, Peng B, Buchdunger E, Ford J *et al*. Bcr-Abl kinase inhibition as the basis of therapy for CML.29th Annual Meeting of the International Society for Experimental Hematology,

Tampa, Florida, USA, July 08-11,#2000; Experimental Hematology:130.

92. Lee SJ, Kuntz KM, Horowitz MM, McGlave PB, Goldman JM, Sobocinski KA, Hegland J, *et al.* Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: a decision analysis. *Ann Intern Med* 1997;127:1080-8.

93. Ohnishi K, Ohno R, Tomonaga M, Kamada N, Onozawa K, Kuramoto A *et al*. A randomized trial comparing interferon- alpha with busulfan for newly diagnosed chronic myelogenous leukemia in chronic phase. *Blood* 1995;86/3:-916.

94. Allan NC, Richards SM, and-Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. *Lancet* 1995;345:1392-7.

95. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. *N Engl J Med* 1994;330:820-5.

96. Sokal JE, Baccarani M, Tura S, Fiacchini M, Cervantes F, Rozman C *et al*. Prognostic discrimination among younger patients with chronic granulocytic leukemia: relevance to bone marrow transplantation. *Blood* 1985;66:1352-7.

97. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK *et al*. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group. *Blood* 1993;82:398-407.

98. Sonnenberg FA,.Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322-38.

99. McGlave P, Bartsch G, Anasetti C, Ash R, Beatty P, Gajewski J *et al*. Unrelated donor marrow transplantation therapy for chronic myelogenous leukemia: initial experience of the National Marrow Donor Program. *Blood* 1993;81:543-50.

100. Lee SJ, Anasetti C, Kuntz KM, Patten J, Antin JH, Weeks JC. The costs and cost-effectiveness of unrelated donor bone marrow transplantation for chronic phase chronic myelogenous leukemia. *Blood* 1998;92:4047-52.

101. Leda M, Ladon D, Pieczonka A, Boruczkowski D, Jolkowska J, Witt M *et al*. Donor lymphocyte infusion followed by interferon-alpha plus low dose cyclosporine A for modulation of donor CD3 cells activity with monitoring of minimal residual disease and cellular chimerism in a

patient with first hematologic relapse of chronic myelogenous leukemia after allogeneic bone marrow transplantation. *Leukemia Research* 2001;25:353-7.

102. Goldman JM, Marin D, Olavarria E, Apperley JF. Clinical decisions for CML in chronic phase - 2003. *Seminar in Hematology (in press)* 2003.

103. Mahon FX, Deininger MWN, Schultheis B, Chabrol J, Reiffers J, Goldman JM *et al*. Selection and characterization of BCR-ABL positive cell lines with differential sensitivity to the tyrosine kinase inhibitor STI571: diverse mechanisms of resistance. *Blood* 2000;96:1070-9.

104. Weisberg E,.[a]. Mechanism of resistance to the ABL tyrosine kinase inhibitor STI571 in BCR/ABL-transformed hematopoietic cell lines. *Blood [print]* 2000;95:3498-505.

105. Gambacorti-Passerini C BRICPZMCGCLeal. Role of alpha1 Acid Glycoprotein in the In Vivo resistance of Human BCR-ABL+leukemic cells to the Abl inhibitor ST1571. *J Natl Cancer Inst* 2000;92:1641-50.

106. Gambacorti-Passerini C, Barni R, Marchesi E, Verga M, Rossi F, Rossi F *et al*. Sensitivity to the abl inhibitor STI571 in fresh leukaemic cells obtained from chronic myelogenous leukaemia patients in different stages of disease. *Br J Haematol* 2001;112:972-4.