Vidaza® (azacitidine) in myelodysplastic syndromes: National Institute for Health and Clinical Excellence re-appraisal

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Executive summary

Following a recent appeal against the negative final appraisal determination (FAD) issued by the National Institute for Health and Clinical Excellence (NICE) for azacitidine (Vidaza®) (March 2010), the NICE Appeal Panel requested the following:

'The Appeal Panel requests the Appraisal Committee to reconsider the guidance issued taking account of both best supportive care and low-dose chemotherapy as comparators. The Appeal Panel also requests the Appraisal Committee to examine the data on quality of life and consider the utilities available to it from MDS UK.'

In this report, Celgene provides the information requested by the NICE Appraisal Committee to enable this further consideration and analysis.

Myelodysplastic syndromes (MDS) are a heterogeneous condition. Previous consideration by NICE revealed a lack of clarity as to the 'standard' treatment of MDS in UK clinical practice. This consideration affects the choice of comparators and subgroups, an important issue in this appraisal because azacitidine's cost-effectiveness estimate appears to be within an acceptable range* when it is limited to a comparison with LDC, carried out in a subpopulation of LDC-eligible patients.

Evidence considered in the Appraisal Committee meetings and Appeal Hearing led to a decision that low-dose chemotherapy (LDC) required further attention as a potential comparator for azacitidine. However, the level of use of LDC in UK clinical practice needs to be further substantiated. To address this need Celgene presents three new pieces of evidence:

- A survey of 72 haematologists
- Interim data from an ongoing hospital survey
- A report from a nationally-recognised registry (Haematological Malignancies Research Network registry, maintained by University of York)

This evidence collectively provides a very strong demonstration of the continuing use of LDC as a treatment option in MDS.

* Providing end-of-life considerations and the ultra-orphan status of the medicine are taken into account

The Institute has also requested further research into how MDS patients are judged to be clinically suitable for treatment with LDC. There is concern not only about the identification of clinical criteria enabling such judgment, but also about the role and influence of patient preference. A medical literature review found that LDC was most commonly administered to MDS patients whose disease was classified as Intermediate-2 or High on the International Prognostic Scoring System (IPSS) and who had the following characteristics:

- Symptomatic cytopenias
  - Anaemia requiring transfusion
  - Neutropenia 0.5-1 x 10^9/l (+/- infectious episodes)
  - Thrombocytopenia 30-100 x 10^9/l
- Normal karyotype (or 1 cytogenetic abnormality)
- Limited co-morbidities with a haematopoietic cell transplantation-specific comorbidity index (HCTCI) score of 0 to 2
- Performance status score of 0-2
- Logistically able to undergo treatment

These findings were supported by results from the survey of 72 haematologists as well as by data from the York registry, which both identified the same haematological criteria. The survey demonstrated the role of patient preference in treatment allocation.

In response to a request from NICE, Celgene has also provided a literature review describing the main concerns facing “patient preference” trials. Papers identified in this review had limited relevance to the pivotal azacitidine trial, AZA-001. In AZA-001 the allocation of patients to active or control treatment was random and the patient’s preference partly influenced which control treatment would be most suitable.

This report also provides two sections already submitted to NICE on 25 August 2010:

- a summary of quality of life research received from the MDS UK patient group
- sensitivity analyses on the NICE-preferred economic model which substitute utility scores for those estimated in this quality of life research

These analyses support the NICE Appraisal Committee’s observation that transfusion independence plays an important role in the life quality of MDS patients which may have been under valued in the original economic model’s utility estimates. However, the limitations of the utility data provided by MDS UK mean that they do not provide a better assessment of life quality gain for use in an economic model.

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Glossary and report notes

List of abbreviations

AE	Adverse event
Ara-C	Cytarabine arabinoside
BFI	Brief Fatigue Inventory
BSC	Supportive care only (best supportive care)
CCI	Charlson Co-Morbidity Index
CEAC	Cost-effectiveness acceptability curve
CMML	Chronic myelomonocytic leukaemia
CR	Complete response
ESA	Erythropoiesis-stimulating agents
FACT-An	Functional Assessment of Cancer Therapy-Anaemia
HCTCI	Haematopoietic cell transplantation-specific comorbidity index
HI	Haematological improvement
HMRN	Haematological Malignancies Research Network
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPSS	International prognostic scoring system
IQR	Interquartile range
LDC	Low-dose chemotherapy (i.e. low-dose Ara-C)
LAS	Godin Leisure Time Activity Score
MDS	Myelodysplastic syndromes
NICE	National Institute for Health and Clinical Excellence
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
RAEB	Refractory anaemia with excess blasts
RBC	Red blood cell
RCT	Randomised controlled trial
SD	Standard deviation
SDC	Standard-dose chemotherapy
WHO	World Health Organization

Reference to low-dose chemotherapy

This treatment is abbreviated as LDC and is described as low-dose chemotherapy in the documents presented. However, to avoid any potential confusion, all of Celgene's communication with clinicians regarding this treatment referred to LDC by its more detailed name: low-dose cytarabine arabinoside (low-dose Ara-C for short).

Document content

Sections 2 and 3 of this report are copies of documentation already sent to NICE on 25 August 2010. They are included here for completeness and to allow the Decision Support Unit and NICE Appraisal Committee to refer to a single document.

Brief "section summaries" at the beginning of each section allow the different aspects of this resubmission to be easily considered separately.

Section 1. The place of LDC in current practice

Section summary

This section incorporates results from a new survey of haematologists, an ongoing Celgene hospital study, data from a nationally recognised registry of haematological malignancies, and a medical literature review.

The research provides strong evidence for the continuing use of LDC in clinical practice, not only in terms of individual clinician's treatment choices but expressed as absolute numbers of patients, although the numbers may not be entirely accurate because of the detailed definition of azacitidine-indicated MDS. The findings support the view of the Appeal Panel on 1 June 2010, who considered that the available evidence at the time did suggest usage of LDC in UK clinical practice.

The new haematologist survey (n=72) provided quantitative evidence, which was backed up by the literature review and the registry data, that suitability for LDC might be determinable using haematological characteristics (transfusion dependence, symptomatic cytopenias, presence of AML, cytogenetic profile). Although no individual clinical characteristic was very strongly associated with suitability for LDC, taken together these criteria form a useful starting point for a consultative process between the clinician and the patient.

The survey also investigated the role of patient preference in decision-making. According to the 72 haematologist respondents, 30 per cent of patients who were considered clinically "appropriate" to receive LDC would subsequently opt not to receive it because of personal preference. These findings show that clinical judgments about LDC suitability are sometimes further influenced by patient preference.

Introduction

This research task had three main aims:

1) Obtain more comprehensive information about levels of use of LDC in UK clinical practice, to reinforce the evidence previously discussed and accepted at the NICE Appeal Hearing for azacitidine.
2) Quantify the degree to which certain clinical characteristics can affect a clinician's decision to pre-select a patient for treatment with LDC.
3) Quantify the extent to which patient preference can influence the final treatment decision with regard to LDC, either positively (i.e. clinically less appropriate for LDC, but receives because of patient preference) or negatively (i.e. clinically suitable for LDC, but does not receive because of patient preference).

To meet these aims, a new survey was undertaken of UK-based haematologists. Additional data sources were identified through a literature search and via existing, ongoing research either funded by Celgene or run by an independent organisation. The new survey was designed to meet all three aims; the other information sources identified were used to contextualise and compare its findings to existing studies in the same field.

Methods

Medical literature review

To ensure that the survey identified all relevant clinical characteristics on which a patient may be pre-selected for LDC, an informal review of the clinical literature was undertaken. The review had the objective of listing any patient clinical characteristics which had been found in existing studies of MDS patients to be associated with better outcomes on LDC treatment.

Haematologist survey (n=72)

To address the research aims, Celgene developed a new survey to be administered to UK haematologists. Item development was guided by the literature review

described above and the final item list was checked by Professor Ghulam Mufti[†]. One important amendment to wording was to consistently refer to low-dose chemotherapy as "low-dose Ara-C"[‡], as "chemotherapy" was felt likely to be misinterpreted by many respondents as pertaining to a more intensive regimen.

Items

Respondents were asked about their practice and judgment on a range of issues related to the study questions. These are as follows:

1) Numbers of patients treated with BSC, LDC, SDC, azacitidine and other treatments
    a) Respondents were asked to estimate these numbers in the years 2008, 2009 and 2010
2) Which clinical characteristics (of those usually measured in MDS patients) would make them more or less likely to treat with LDC
3) The proportion of patients judged to be clinically "appropriate", "inappropriate" or "borderline" for treatment with LDC
4) The proportion of cases in which a patient's preference would override the above clinical judgments of eligibility for LDC

The full list of survey items is spelled out alongside the raw results from the survey in Appendix 2.

Responses were captured as continuous or categorical variables as appropriate. Five-point Likert scales were used in the questions relating to judgment of clinical characteristics.

Recruitment

Survey invitations were circulated via two methods: firstly the contacts database of a commercial survey company, and secondly through the mailing list of the UK MDS forum, a non-governmental organisation whose clinician members have a special

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[†] Ghulam Mufti is Professor of Haematological Medicine and Head of Haematology Department at King's College London Hospital. He is a member of the European Bone Marrow Transplantation Group and a founding member of the Board of the International Myelodysplastic Foundation of which his Department at King's College Hospital is a recognised Centre of Excellence. He is also Chair of the UK MDS Forum.

[‡] Ara-C = cytarabine arabinoside

interest in MDS. Some respondents were identifiable as “key opinion leaders” or specialist consultants.

Celgene hospital study (n=23 hospitals) and York registry (n=22 hospitals)

A second, ongoing study being conducted by Celgene includes a similar set of variables relating to current use of treatments in MDS as posed in question 1 of the main (n=72) survey. Responses were collected at the hospital level. Similar to the haematologist survey, the Celgene ongoing study allows distinction of “MDS specialist” hospitals.

The University of York maintains a registry via its Haematological Malignancies Research Network (HMRN), which is currently collecting data from 22 UK hospitals. The registry automatically captures information about the distribution of treatments given to MDS patients and this information has been summarised. The registry also records the clinical characteristics of patients.

Both the Celgene hospital study and the York Registry relate to the treatment of all MDS, rather than the azacitidine-eligible subpopulation[§].

Analysis and presentation of results

Results from all three studies are presented together under the relevant themes. Simple descriptive statistics are used for continuous and categorical variables. Tabulations and graphics are provided where appropriate. The Results only presents figures most relevant to the study questions. A more comprehensive summary of results from the haematologist survey and York Registry can be found in the Appendix.

Treatment allocation statistics are displayed in two ways:

1) As an aggregate total number of patients divided according to the treatment they received (shows overall usage of the treatment options in the sample)
2) As a distribution of the percentage of patients reported by each respondent (shows individual variation in treatment allocation)

[§] SPC license indication here

A linear regression analysis was performed on the survey data to assess any trends over time in the number of patients the haematologists allocated to the various treatment options. Standard errors were controlled for the repeated measurements within each haematologist.

Results

Medical literature review

Low dose chemotherapy has been used for the treatment of myelodysplastic syndromes for over thirty years[37-45] with several trials showing response rates of approximately 15% complete response (CR), 20% partial response (PR) and 20% haematological improvement (HI). While responders may show an increase in survival there has been no consistent demonstration that these response rates show a benefit in terms of overall survival and transformation to AML compared to best supportive care.

The blast count for inclusion in these studies varied between 10%-30% but other consistent criteria were:

- Transfusion dependent anaemia (various definitions ranging from a documented requirement over three months to more than two units of packed red blood cells within the preceding six weeks)
- Thrombocytopenia 30-100 x 10^9/l
- Neutropenia 0.5-1 x 10^9/l

There are a number of other factors that may determine a patient's suitability for LDC:

- Normal karyotype is associated with a better outcome while the presence of ≥ 2 cytogenetic abnormalities is associated with a poor response.[46]
- Significant toxicity, particularly infection associated with neutropenia, and toxic death has been reported in up to 15% of patients.[47]
- Administration is 10mg/m^2 subcutaneously twice daily days 1-14 which has significant logistic implications in that the patient may either have to be admitted or attend a day ward if healthcare at home is not feasible
- Presence and extent of any co-morbidities

Co-morbidities are an important factor in selecting patients for LDC as the ability of a patient to deal with toxicity, in particular, has a significant impact on the eventual outcome of treatment. This is also true in patients undergoing haematopoietic stem cell transplant and intensive chemotherapy. In this situation, there have been attempts to evaluate the impact of different co-morbidities on outcome. The most recent of these is the Haematopoietic cell transplantation-specific comorbidity index (HCTCI)[48] which provides valid and reliable scoring of co- morbidities that predicted non-relapse mortality and survival in stem cell transplantation and intensive chemotherapy.[49] The HCTCI has also been shown to have prognostic relevance in International Prognostic Scoring System (IPSS) intermediate- and high- risk MDS, clearly distinguishing between low-, intermediate- and high-risk patients treated with best supportive care.[50] The HCTCI is not currently in routine clinical use in the UK in this situation but, with validation compared to LDC, may provide a method of more consistently assessing the impact of co-morbidities on treatment outcome than clinical judgment.

Taking these various factors into account LDC is most widely used in the UK in MDS patients with IPSS INT-2 / High and the following characteristics:

- Symptomatic cytopenias
  - Anaemia requiring transfusion
  - Neutropenia 0.5-1 x 10^9/l (+/- infectious episodes)
  - Thrombocytopenia 30-100 x 10^9/l
- Normal karyotype (or 1 cytogenetic abnormality)
- Limited co-morbidities (HCTCI score 0-2)
- Performance status 0-2
- Logistically able to undergo treatment

These clinical characteristics and others identified through the assistance of Ghulam Mufti were included in the haematologist survey. Co-morbidities were evaluated as individual conditions rather than an aggregate score.

Recruitment results

A total 72 haematologists responded to the survey (10 responded via the MDS Forum mailing list, 62 responded from the commercial database contact list). Five respondents were identified as specialist consultants or “key opinion leaders” (KOL).

The Celgene hospital study had investigated 23 hospitals at the time of analysis, of which 8 were specialist MDS centres. Reponses to this study described the current management of 2,444 patients, of which 728 were being seen in specialist centres.

The York registry yielded usable information about 22 hospitals, relating to the management of 91 patients with CMML, 626 patients with MDS and 664 patients with AML (total 1,381).

Current treatment allocation in MDS

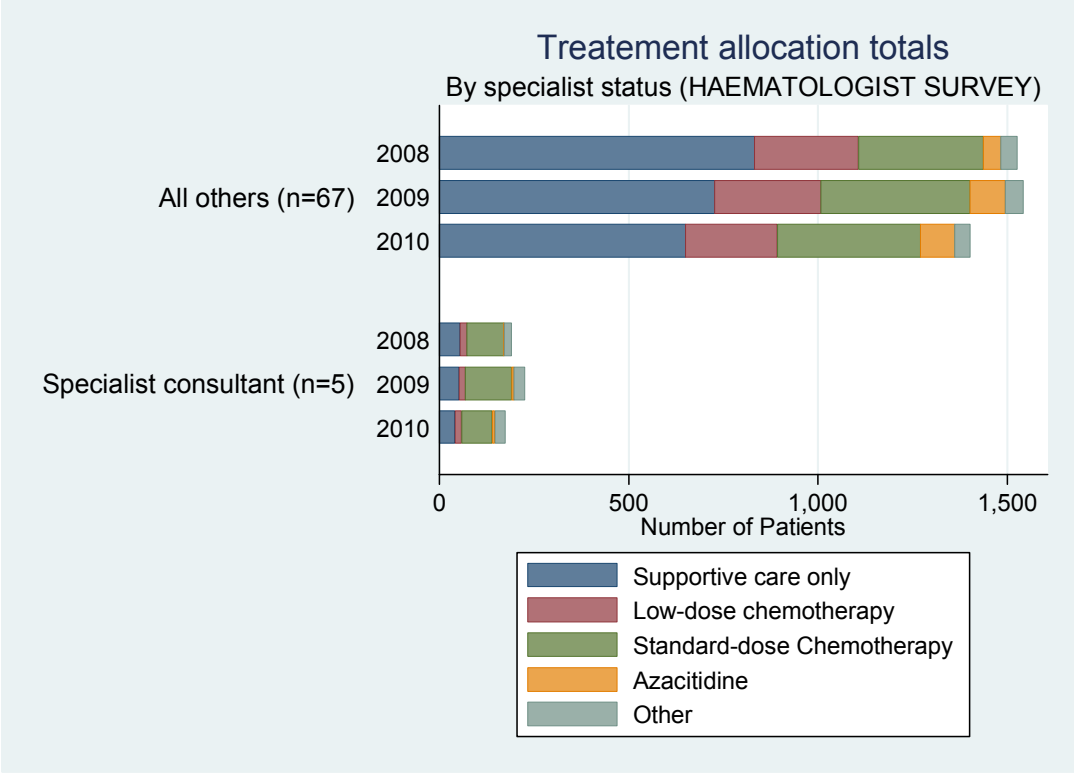
All three pieces of research (haematologist survey, Celgene hospital study and York Registry) allowed the estimation of total patient numbers according to treatment administered. The survey further allowed presentation to be separated by year. These results are presented, separated by "specialist" status or disease subtype in Figure 4.1, Figure 4.2 and Figure 4.3. Each study showed that low-dose chemotherapy was used at modest levels in all settings, whether for the whole MDS population or just for the azacitidine-indicated subpopulation of MDS, chronic myelomonocytic leukaemia (CMML) and AML.

The haematologist survey data (Figure 4.1) suggest no notable trends over time in the number of patients assigned to LDC or SDC. However there is evidence to suggest an annual average reduction in the numbers of patients given BSC (β_{year}=-1.35 patients per annum per haematologist, $p<0.001$). The change in azacitidine prescribing attained borderline statistical significance (β_{year}=0.35 patients per annum per haematologist, $p<0.05$). Patients treated by the five specialist consultants seemed less likely to receive LDC, but overall the differences in treatment allocation between specialists were not statistically significant.

Celgene hospital study data (Figure 4.2) reflected a similar distribution as seen in the haematologist survey, except that specialist centres tended to give a greater proportion of total patients LDC than did the non-specialist centres (in the haematologist survey, non-specialists gave the most LDC). Also, the treated population was larger as the Celgene hospital study relates to all MDS patients, not just those indicated for azacitidine. The York Registry figures broadly support these findings, although as can be seen the data provided by York distinguish patients

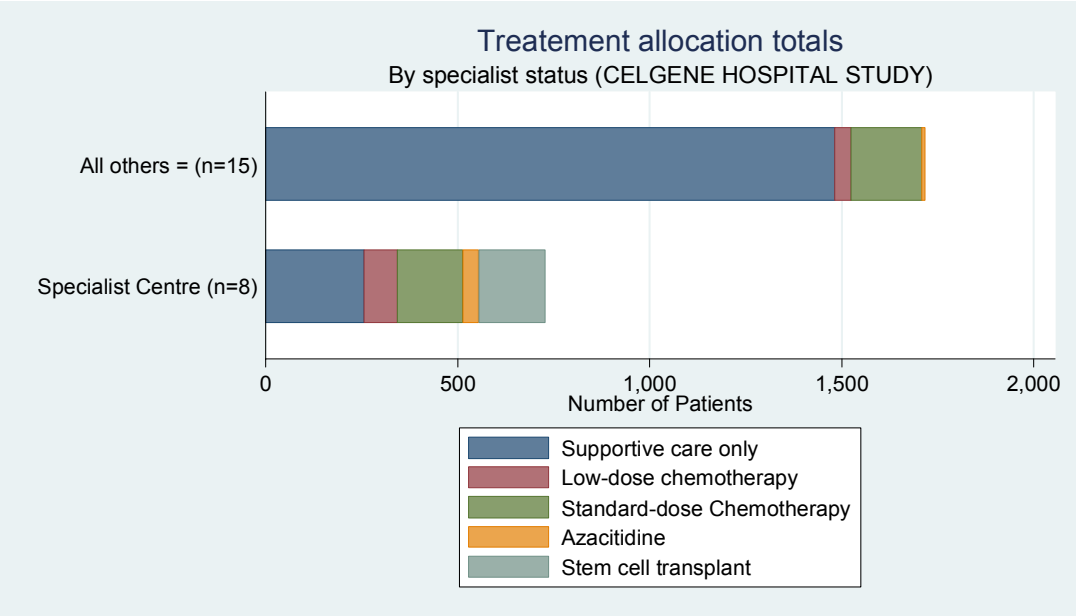
according to haematological malignancy in a way which is not entirely compatible with the study questions.

Figure 4.1. Haematologist survey totals



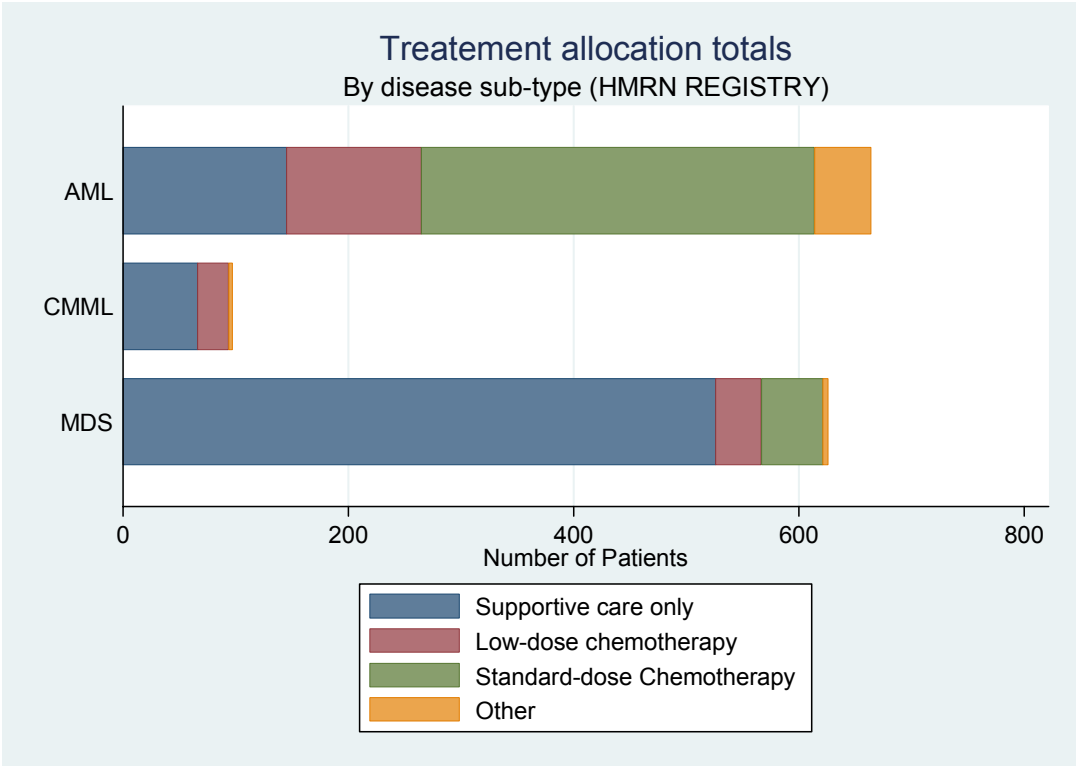
NOTE: Each bar represents total numbers of patients coloured according to treatment allocation.

Figure 4.1. Celgene hospital study totals



NOTE: this study relates to the entire MDS disease definition, not just the azacitidine-eligible portion. Each bar represents total numbers of patients coloured according to treatment allocation.

Figure 4.2. York (HMRN) registry totals

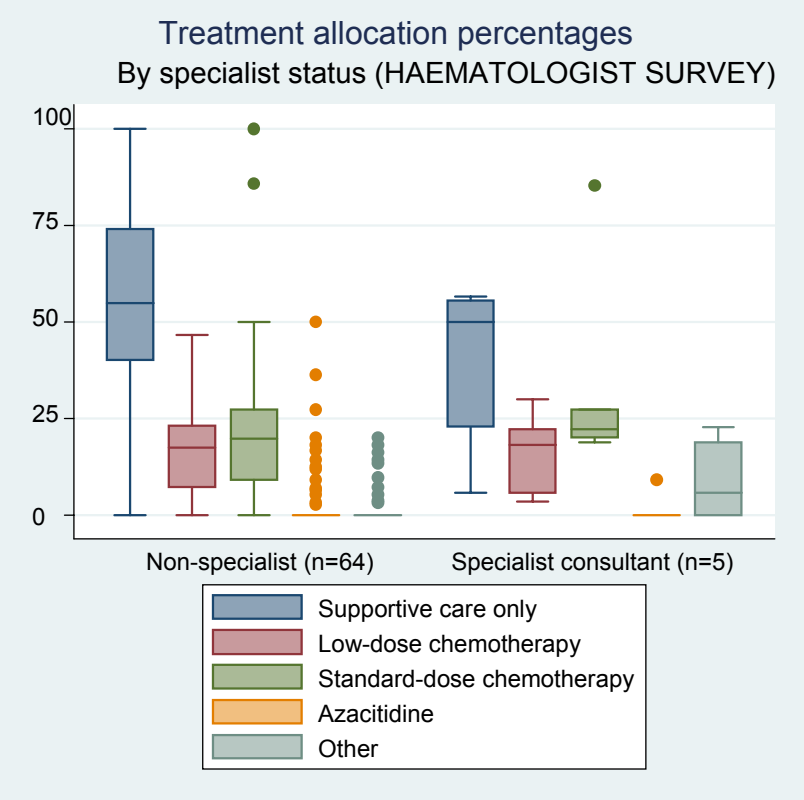


NOTE: this study relates to the entire MDS disease definition, not just the azacitidine-eligible portion. Each bar represents total numbers of patients coloured according to treatment allocation.
AML = acute myeloid leukaemia, CMML = chronic myelomonocytic leukaemia, MDS = myelodysplastic syndromes.

Treatment allocation variation

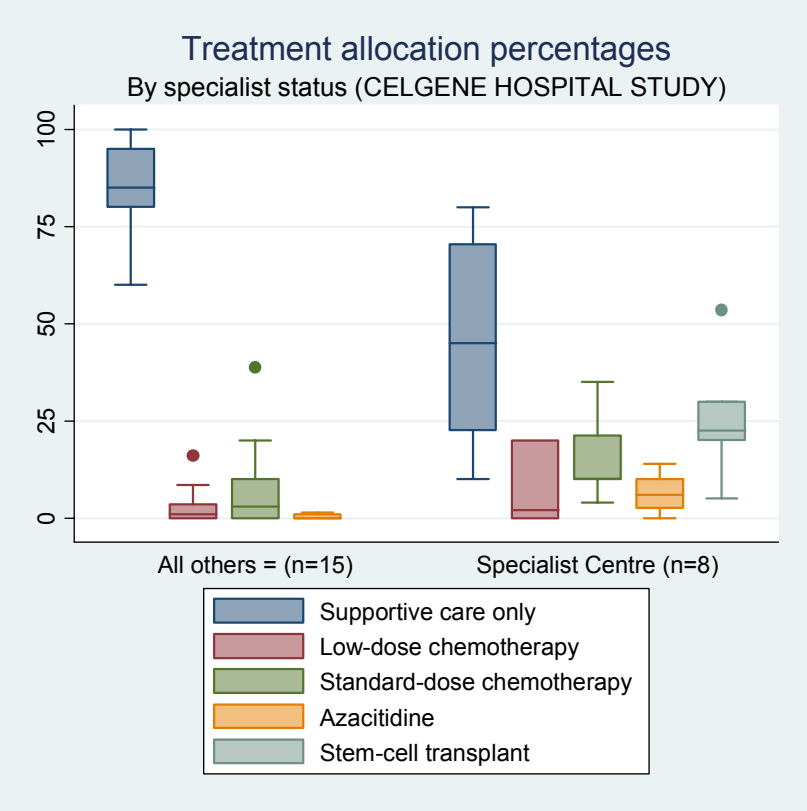
Variation in treatment allocation could be estimated in the haematologist survey and Celgene hospital study. This variation is summarised in box plots for the 72 haematologists[**] in Figure 4.4 and for the 22 hospitals in Figure 4.5. The two graphics support two main findings. Firstly, there is variation in treatment allocation practice between practitioners at all levels, be it hospital or individual. Specialist and non-specialist centres/haematologists are also found to differ. Secondly, specialist centres/haematologists generally tend assign a smaller proportion of patients to BSC alone. LDC use seemed to be less commonly chosen in the hospital study than in the haematologist survey; this may be attributable to the wider patient population covered by the hospital study (namely, all MDS patients, not just azacitidine-indicated). The haematologist survey suggested that the majority of respondents would elect to give LDC to a small proportion of patients (median for all haematologists = 18% of patients, IQR= 5.7%, 23.1%). This statistic is broken down more finely in the Appendix.

Figure 4.3. Haematologist survey percentages



[**] The 2010 figures are used for the box plot.

Figure 4.4. Celgene hospital study percentages



Clinical characteristics associated with use of LDC

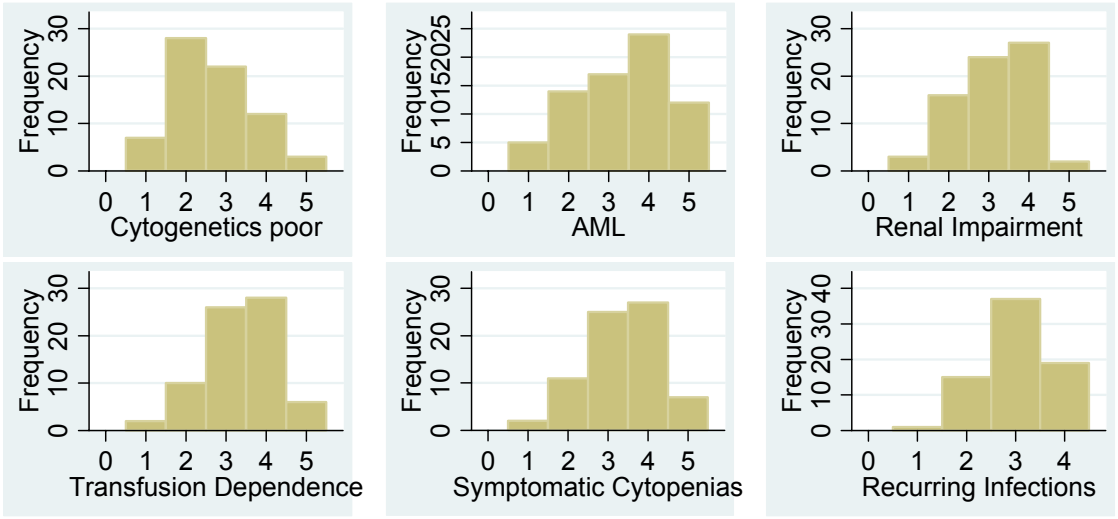
The haematologist survey asked respondents to rate a set of clinical characteristics relevant to MDS. Each characteristic was rated according to its influence on a patient's "clinical suitability" to receive LDC as opposed to BSC or SDC. Characteristics scored with a 4 or 5 are respectively likely or very likely to make a patient clinically suitable for LDC. Characteristics scored with a 1 or 2 are respectively very unlikely or unlikely to make a patient clinically suitable. A score of 3 indicates that the clinical characteristic has little or no influence on clinical suitability ("neither likely nor unlikely").

Most clinical characteristics showed great variation in how they were rated. Clinical characteristics for which the skewness statistic was greater than 0.25 in magnitude are presented in Figure 4.6.

Patients with poor cytogenetics were less likely to be judged appropriate for LDC (48% "unlikely" or "very unlikely" versus 20% "likely" or "very likely"). All other clinical characteristics identified had a positive association with pre-selection for LDC (AML

50% positive vs. 26% negative; renal impairment 40% vs. 26%; transfusion dependence 47% vs. 17%; symptomatic cytopenias 47% vs. 18%; recurring infections 26% vs. 22%). The recurring infections characteristic met the criteria for inclusion in the results, but clinically the distinction afforded by this variable is very slight.

Figure 4.5. Ratings of Clinical Characteristics from Haematologist Survey



NOTE: Response categories were 1 "very unlikely, 2 "unlikely", 3 "neither likely nor unlikely", 4 "likely", 5 "very likely". Exact question wording: *Please review the following list of the clinical criteria which may be used in selecting patients to receive low-dose Ara-C [low-dose chemotherapy], and indicate how likely each of these characteristics would be to lead you to decide that a patient is clinically suitable for low-dose Ara-C rather than supportive care or standard dose chemotherapy.*

The York Registry provided a breakdown of treatment allocation by a set of clinical characteristics being collected in the database. Although the full dataset was not provided for further analysis, the results for the MDS population in this registry suggest the following trends:

- The rate of treatment with LDC is increased if a patient has 2 or more cytopenias (around 4% for 0-1 cytopenias, around 9% for 2-3 cytopenias)
- Higher IPSS[††] risk category is positively associated with use of LDC, however the use of all treatments including transfusions increases along with this characteristic
- Having a World Health Organisation (WHO) disease subtype classification of Refractory anaemia with excess blasts (RAEB) was associated with increased usage of both LDC and SDC

[††] International Prognostic Scoring System for MDS

- Patients receiving LDC had a median age of 77 compared to 80 years for patients receiving BSC, and patients receiving SDC had a median age of 59; age ranges were very wide in all treatment options and overlapped

The full tabulations provided by the HMRN for the York Registry are provided in the Appendix.

Role of patient preference

The last two parts of the haematologist survey estimated the relative frequency with which patients would be clinically regarded as "appropriate", "inappropriate" or "borderline" for treatment with LDC. Respondents were then asked to indicate the relative frequency at which patients might subsequently receive or not receive LDC, given their clinical rating for LDC. The purpose of this part of the survey was to quantify the influence of patient preference on decisions, as reflected in the survey wording. Results are summarised in Table 4.1. The means in the table suggest that patient preference plays an important role in allocation to LDC, in addition to clinical judgment alone. Statistics in this table suggest that, on average, haematologists would allow 35% of patients they had deemed clinically "inappropriate" for LDC to proceed with LDC treatment anyway, because of the patient's stated preference. Similarly, the average haematologist would allow about 30% of patients regarded as "clinically appropriate" for LDC to forego the treatment after accounting for personal preference. 95% confidence intervals for these averages are relatively narrow (usually less than 10% in either direction), suggesting a reasonable level of agreement between doctors on these questions. The percentages do not add up to 100, meaning that a proportion of patients have an unknown final treatment allocation in these hypothetical scenarios.

Table 4.1. Clinical pre-selection and patient preference influence

Clinical suitability for LDC	Relative frequency of reporting (%)	Subsequent LDC use accounting for patient preference	
		Yes (%)	No (%)
"Appropriate"	36.2 (31.2, 41.3)	44.4 (37.5, 51.3)	29.1 (22.5, 35.8)
"Inappropriate"	47.6 (42.4, 52.7)	35.8 (29.4, 42.2)	32.3 (25.8, 38.8)
"Borderline"	23.0 (19.1, 26.9)	26.2 (19.6, 32.7)	31.6 (23.9, 39.3)

NOTE: All responses were percentages; each cell contains mean (95% CI)

Discussion

The combined research into the place of LDC in UK clinical practice had three main aims:

1) Quantify the level of LDC use in UK clinical practice
2) Quantify the association of the patient clinical characteristics with pre-selection for LDC treatment
3) Quantify the influence of patient preference on treatment allocation (specifically to LDC)

Results relating to the first question corroborate the evidence considered and accepted at the NICE appeal for azacitidine on 1 June 2010. This evidence was accepted by the Appeal Panel as reflecting the routine use of LDC. The current survey findings indicate that a small but steady (over time) number of MDS patients are receiving LDC. This finding is reflected not only in the treatment allocation percentages reported, but also when translated to an absolute number of patients. The absolute numbers of MDS patients from the survey appears slightly higher than might be expected given the incidence and prevalence of azacitidine-eligible MDS – this is probably explained by the fact that several clinicians will have treated the same patients, and could also reflect some confusion as to MDS diagnosis. Results were slightly different in the Celgene hospital study and York registry, but this may be attributed to the wider definition of MDS used in both these studies which includes many more patients with asymptomatic or mildly symptomatic disease, i.e. not the azacitidine-eligible population.

The haematologist survey questions relating to clinical characteristics supported the findings from the medical literature review for most characteristics. The main clinical characteristics found to influence the judgment of clinical suitability for LDC were haematological:

- Symptomatic cytopenias (positive influence)
- Transfusion dependence (positive influence)
- AML (positive influence)
- Cytogenetic profile = poor (negative influences)

In the survey, renal failure and persistent infections were also positively associated with LDC suitability. The influence of “Infections” was very slight and probably

already adequately captured in the “symptomatic cytopenias” criterion. Renal failure was not identified in the literature as an important predictor of LDC suitability and should be treated with caution. The findings from the survey on clinical characteristics also shared some similarities with data from the York registry, although this registry did not provide any insight into actual decision-making: it simply reflected the final treatment allocation and recorded basic patient characteristics.

The responses given to questions regarding patient preference afford an insight into how often MDS patients can shape the treatment decisions for themselves, independently of any clinical judgment. Discounting the “borderline” classification, it seems that around 30% to 35% of MDS patients prefer (and receive) a treatment allocation that contradicts the clinical pre-judgment as to their suitability for LDC.

Methodological considerations

The haematologist survey, Celgene hospital study and York registry have certain attributes which may impact on their application to the current topic. These are summarised in the following bullet points:

- The York registry and Celgene hospital study do not relate directly to the azacitidine-indicated MDS population but rather a wider group of MDS patients who have milder disease and therefore may be associated with slightly different treatment allocation.
- The sample of haematologists provided in the new survey are distinguished by “MDS specialist” status only in a very limited number of cases and the group generally is not identifiable due to a confidentiality agreement between the commercial research company and the respondents; therefore the degree of experience the respondents have in treating MDS is unknown for the majority. Given that some variation was observed between the small number of MDS specialist clinicians/hospitals and the non-MDS specialists, it could be that the results disguise informative differences in prescribing practice between different groups of clinicians. However, a diagnostic analysis comparing all results by **source** (whether the data came from the MDS Forum mailing list of the survey company list) revealed no differences in the distribution of LDC usage.
- MDS is a heterogeneous disease, and clinicians apparently vary in the way they approach the disease, so quantitative estimates based on clinical practice decisions are always likely to come with considerable variance.

- The clinical characteristics questions provide a sound base for discussion on the formation of criteria for LDC suitability. But the statistics suggest that considering any one characteristic in isolation is not wholly compatible with the multi-faceted approach to clinical decision-making in which multiple criteria may have an influence on the final decision which is greater (or smaller, depending on interactions) than the sum of its parts.

Conclusion

The combined evidence presented in this section serves to reinforce previous conclusions of the Appeal Panel regarding the levels of usage of LDC in UK clinical practice. It was also possible to identify clinical characteristics which seem to be regularly used in identifying patients who are suitable to receive LDC. These clinical characteristics were seen not only in survey results but were also backed up by findings from a literature review and partially reflected in a large, nationally recognised registry.

The research on the role of patient preference indicates that in about 30% of cases, clinical pre-judgments (positive or negative) about clinical suitability for LDC may be overridden if the patient states a preference regarding proceeding with LDC treatment. Defining an LDC-eligible subgroup on the basis of clinical criteria should therefore be approached while maintaining an awareness of this aspect.

In combination, the findings from this section are expected to provide a useful reference for discussion about the establishment of clinical criteria for LDC suitability.

Section 2. Revised economic model for azacitidine (Vidaza®)

Section summary

This section provides up-to-date economic modelling results to assist decision-making as required by the appeal decision. Economic modelling results are presented for low-dose chemotherapy (LDC) and best supportive care (BSC) comparisons. A comparison against 'blended' standard treatments is also presented (that is, incremental costs and benefits averaged across all comparisons according to the relative frequency of comparator treatments observed in the AZA-001 trial).

As per the economic model considered in the FAD,[*] the incremental cost-effectiveness ratio (ICER) for azacitidine was £49,030 compared to LDC and £63,177 compared to BSC. The ICER for azacitidine compared to 'blended' standard treatments was £56,945. This 'blended' ICER was calculated at the request of the Appraisal Committee.

Modelling MDS UK quality of life data

Transfusion independence was thought to have been under-reflected in the model considered in the FAD, which may have led to an underestimation of cost-effectiveness. New data from a study by MDS UK allow assessment of utility according to transfusion status, and provide further evidence about the symptom burden of myelodysplastic syndromes (MDS) and the impact on quality of life of these symptoms.

The provided analyses explore the impact of incorporating the quality of life data from this study. Using the UK-specific utilities from this study, the ICER for azacitidine was £51,117 compared with LDC and £66,092 compared with BSC. The ICER for azacitidine compared to 'blended' standard treatments was £58,290. In this alternative utility model, the ICERs are slightly higher because those patients in the azacitidine arm who remain transfusion dependent do experience survival benefit

[*] That is, the economic model regarded as most plausible by the Evidence Review Group and Appraisal Committee: comparing azacitidine separately with BSC, LDC and standard dose chemotherapy (SDC), using the Weibull survival extrapolation method, and a 7% discount on azacitidine price via a patient access scheme, with no vial sharing assumed and utilities mapped from trial-based quality of life data via oesophageal cancer algorithm.

compared to the standard treatments, but at the same level of utility as applied in the comparator arms.

Both the original Celgene utilities and those obtained via MDS UK have advantages and disadvantages. The Celgene utilities were based on quality of life questionnaires administered in a trial comparing azacitidine and conventional care in the treatment of MDS patients. Azacitidine and conventional care specific questionnaire scores were collected at various time points throughout the trial. As pointed out in the appeal, this quality of life questionnaire had the benefit of being administered in a trial population, but it did not explicitly capture transfusion independence despite the importance of this outcome to MDS patients. Furthermore, utility was derived from the questionnaire scores by way of a mapping algorithm originally developed for another cancer type (oesophageal). By contrast, the MDS UK utilities are based on transfusion status alone and do not distinguish patients according to the treatment(s) they received, nor do the utilities vary over time. This means that any other utility benefits associated with azacitidine treatment, other than transfusion independence, may have been insufficiently captured. Both Celgene and MDS UK utilities were gathered from the whole MDS patient population rather than the azacitidine-indicated high-risk population only.

On balance, the Celgene utilities are likely to be more appropriate for use in a base case, since they were collected in a population of MDS patients who were receiving either azacitidine or conventional care. To some extent transfusion status would have been captured in the dimensions of the questionnaire administered, though probably not fully. The MDS UK utilities provide an important illustration of how important transfusion independence is to the quality of life of MDS patients.
Key findings from this re-analysis are as follows.

- Utilities calculated in the original Celgene model were not dissimilar to those obtained in the MDS UK study. However, other utility benefits associated with treatment (such as relief from depression and anaemia-related fatigue, ability to work and so on) are not captured in the MDS UK study.
- It seems likely that transfusion independence alone would have accounted for a substantial proportion of the quality-adjusted life-year (QALY) benefits seen in the original model.
- The Appraisal Committee were justified in their assertion that the utility gain for azacitidine may be underestimated in the original Celgene model, as the original

quality of life scores and mapped utility estimates did not directly capture the impact of transfusion independence in MDS.

Conclusion

The updated results emphasise that the cost-effectiveness of azacitidine in MDS varies according to the patient's pre-selection to either BSC or LDC. Azacitidine patients pre-selected and then compared with LDC were considerably more cost-effective to treat than patients pre-selected to receive BSC. As identified in the Appeal Decision, as well as by the survey research undertaken by Celgene, LDC is a valid active treatment choice in UK clinical practice. Patients who are eligible to receive LDC form an important subgroup in which the clinical and cost-effectiveness of azacitidine may be assessed.

All cost-effectiveness results have been provided without taking into consideration the National Institute for Health and Clinical Excellence guide to appraising life-extending, end-of-life medicines.

The new cost-effectiveness estimates, based on MDS UK utility scores, help to address uncertainty around the utility estimates in Celgene's original economic model. The results confirm that transfusion dependence/independence status can have a powerful impact on the quality of life of MDS patients, even before other treatment-related benefits (such as relief of anaemic symptoms, even in transfusion-dependent patients) are taken into account. On balance, the trial-based quality of life scores presented in the Celgene submission provide a more detailed set of QALY estimates which are treatment specific.

Introduction

This section presents comprehensive results from Celgene's most up-to-date base case model, including LDC and BSC comparisons, as well as a comparison against 'blended' standard treatments (that is, costs and benefits averaged according to the relative frequency of comparator treatments observed in the AZA-001 trial). These results have already been presented to the National Institute for Health and Clinical Excellence (NICE) in company submissions and appraisal consultation document responses, but they are replicated here for ease of reference.

A scenario analysis that explores the impact of incorporating utility data from a study submitted by MDS UK is also presented. These data are based on the transfusion status (transfusion independent or transfusion dependent) of patients with MDS as reported in Szende *et al* (2009);[1] further detail is presented under the relevant heading.

Base case

Method

The base case analysis results are presented in Table 1.1. This analysis takes into account the NICE preferred base case assumption of a Weibull curve fit to survival data, no vial sharing and a patient access scheme discount of 7% to the acquisition cost of azacitidine.

Table 1.1. Summary of base case cost-effectiveness results

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Pre-selected for BSC					
Azacitidine	£91,753	2.04	£63,756	1.01	£63,177
BSC	£27,998	1.03			
Pre-selected for LDC					
Azacitidine	£101,355	2.44	£65,671	1.34	£49,030
LDC	£35,684	1.10			
'Blended comparison' (that is, azacitidine versus weighted average of BSC, LDC and SDC)					
Azacitidine	£94,146	2.13	£61,801	1.09	£56,945
ALL CCR	£32,345	1.04			
NOTE: BSC = best supportive care; CCR = conventional care regimens; LDC = low-dose chemotherapy; QALY = quality-adjusted life-year; SDC = standard dose chemotherapy					

Results

The results show that treatment with azacitidine results in an increase in discounted lifetime costs of £65,671 compared with treatment with LDC, and £63,756 compared with treatment with BSC. The increased costs were associated with a discounted lifetime gain of 1.34 QALYs compared with LDC and 1.01 QALYs compared with BSC. This results in an ICER of £49,030 compared with LDC and £63,177 compared with BSC. A detailed breakdown of the LDC and BSC comparisons is presented in Tables 1.2 and 1.3.

A ‘blended’ ICER is also presented; this is based on a weighted average of the marginal costs and QALYs estimated for the base case comparisons of azacitidine with LDC, BSC and standard dose chemotherapy (SDC). The weightings applied were consistent with the patient allocation observed in the AZA-001 trial, specifically 62% for BSC, 26% for LDC and 12% for SDC.

Table 1.2. Detailed breakdown of costs for comparison between azacitidine and BSC

Item	Azacitidine (pre-selected for BSC)				BSC		
	In MDS on treatment	In MDS off treatment	In AML	Total	In MDS off treatment	In AML	Total
Cost	£62,004	£19,910	£9,839	£91,753	£18,554	£9,443	£27,998
Premedication	£483			£483			£0
Treatment administration	£2,514	£681		£3,194	£579		£579
Pharmacology	£42,262			£42,262			£0
Follow-up appointments	£2,502	£2,966		£5,468	£2,522		£2,522
Blood/platelet transfusion	£7,256	£8,601		£15,857	£8,938		£8,938
Concurrent medication on treatment	£1,343			£1,343	£989		£989
Concurrent medication off treatment		£1,163		£1,163			£0
Routine tests on treatment	£629			£629	£444		£444
Routine tests off treatment		£522		£522			£0
AML treatment				£0			£0
Follow-up appointments			£1,688	£1,688		£1,620	£1,620
Adverse events			£2,594	£2,594		£2,490	£2,490
Concurrent medication			£768	£768		£738	£738
Blood/platelet transfusion			£4,562	£4,562		£4,378	£4,378
Routine tests			£226	£226		£217	£217
Adverse events	£5,016	£5,978		£10,994	£5,083		£5,083

NOTE: AML = acute myeloid leukaemia; BSC = best supportive care; MDS = myelodysplastic syndrome

Table 1.3. Detailed breakdown of costs for comparison between azacitidine and LDC

Item	Azacitidine (pre-selected for LDC)				LDC			
	In MDS on treatment	In MDS off treatment	In AML	Total	In MDS on treatment	In MDS off treatment	In AML	Total
Cost	£63,948	£28,027	£9,380	£101,355	£15,022	£10,989	£9,673	£35,684
Premedication	£496			£496	£42	£271		£313
Treatment administration	£2,584	£958		£3,542	£1,099			£1,099
Pharmacology	£43,443			£43,443	£112			£112
Follow-up appointments	£2,572	£4,175		£6,747	£1,458	£1,182		£2,641
Blood/platelet transfusion	£7,459	£12,107		£19,566	£7,995	£6,481		£14,476
Concurrent medication on treatment	£1,380			£1,380	£823			£823
Concurrent medication off treatment		£1,637		£1,637		£464		£464
Routine tests on treatment	£647			£647	£336			£336
Routine tests off treatment		£735		£735		£208		£208
AML treatment				£0				£0
Follow-up appointments			£1,609	£1,609			£1,660	£1,660
Adverse events			£2,473	£2,473			£2,550	£2,550
Concurrent medication			£733	£733			£756	£756
Blood/platelet transfusion			£4,349	£4,349			£4,485	£4,485
Routine tests			£216	£216			£223	£223
Adverse events	£5,367	£8,415		£13,783	£3,155	£2,383		£5,538

NOTE: AML = acute myeloid leukaemia; LDC = low-dose chemotherapy; MDS = myelodysplastic syndrome

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to examine the combined effect of uncertainty in all variable input parameters. Values were sampled from the uncertainty distributions associated with each parameter, as set out in the original Celgene submission.

In the PSA, 10,000 sets of parameters were estimated and the marginal costs and QALYs calculated. The results of these analyses are presented as scatter plots in Figures 1.1–1.3 and cost-effectiveness acceptability curves (CEACs) are presented in Figures 1.4–1.6.

The results of the PSA show that azacitidine has an ICER below a threshold of £50,000 on 32% of occasions compared with BSC and 52% of occasions compared with LDC.

Figure 1.1. Scatter plot: PSA results for azacitidine versus BSC

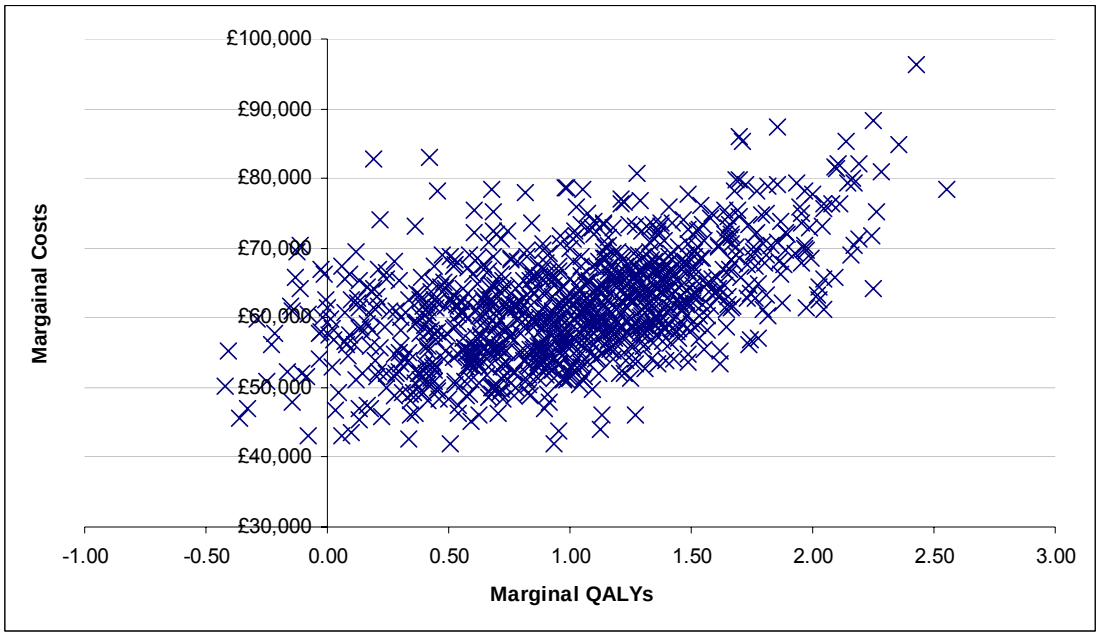


Figure 1.2. Scatter plot: PSA results for azacitidine versus LDC

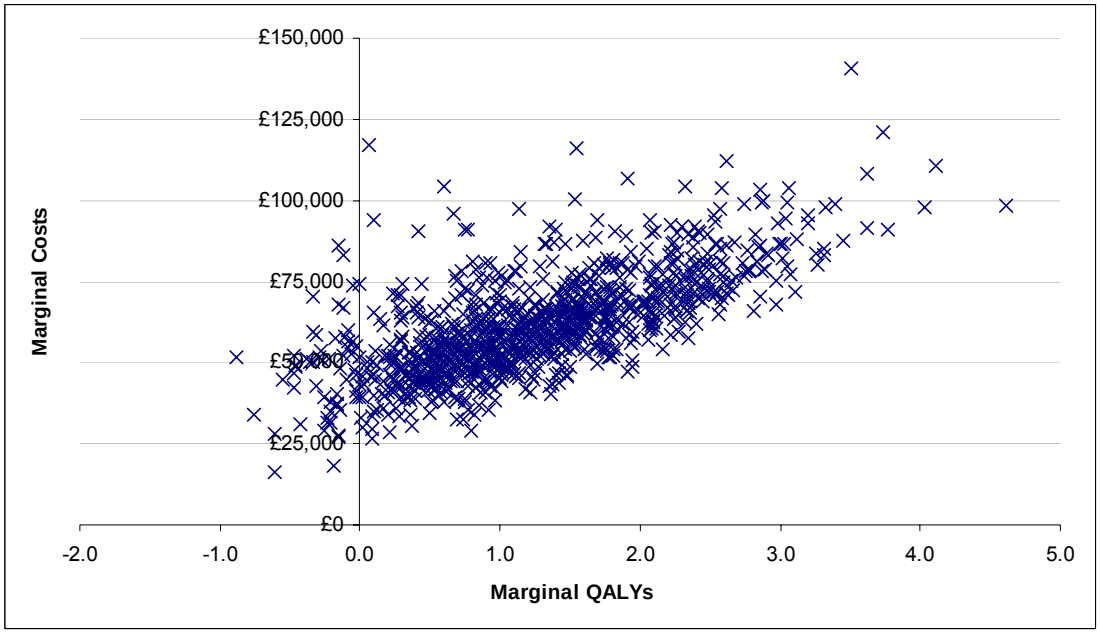


Figure 1.3. Scatter plot: PSA results for azacitidine versus 'blended' comparators

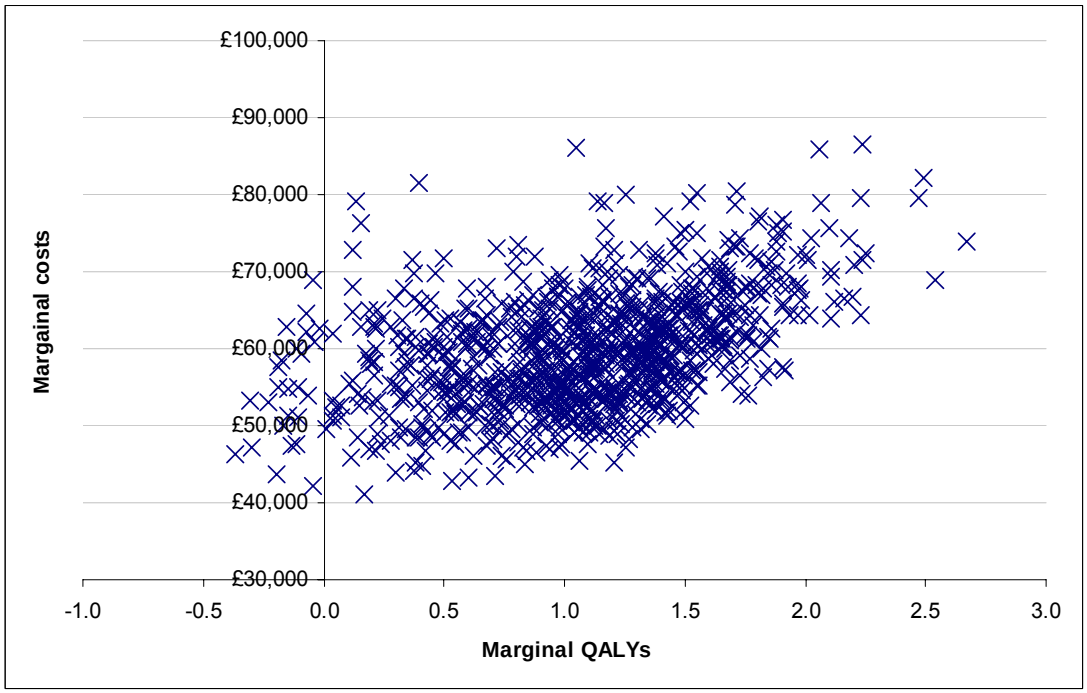


Figure 1.4. CEAC for azacitidine versus BSC

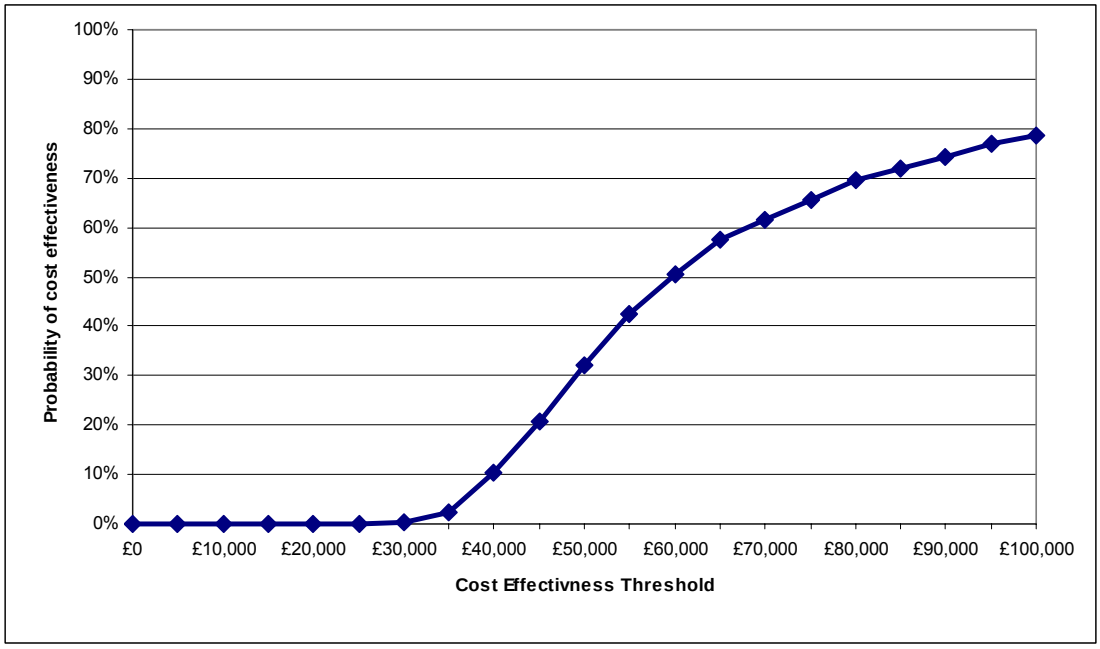


Figure 1.5. CEAC for azacitidine versus LDC

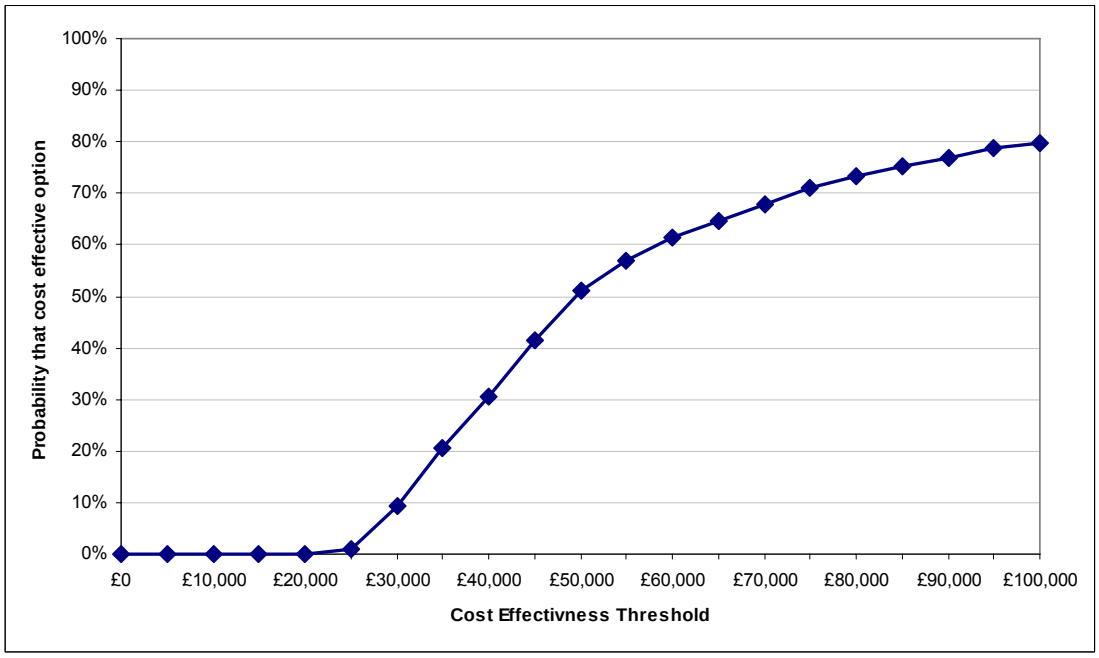
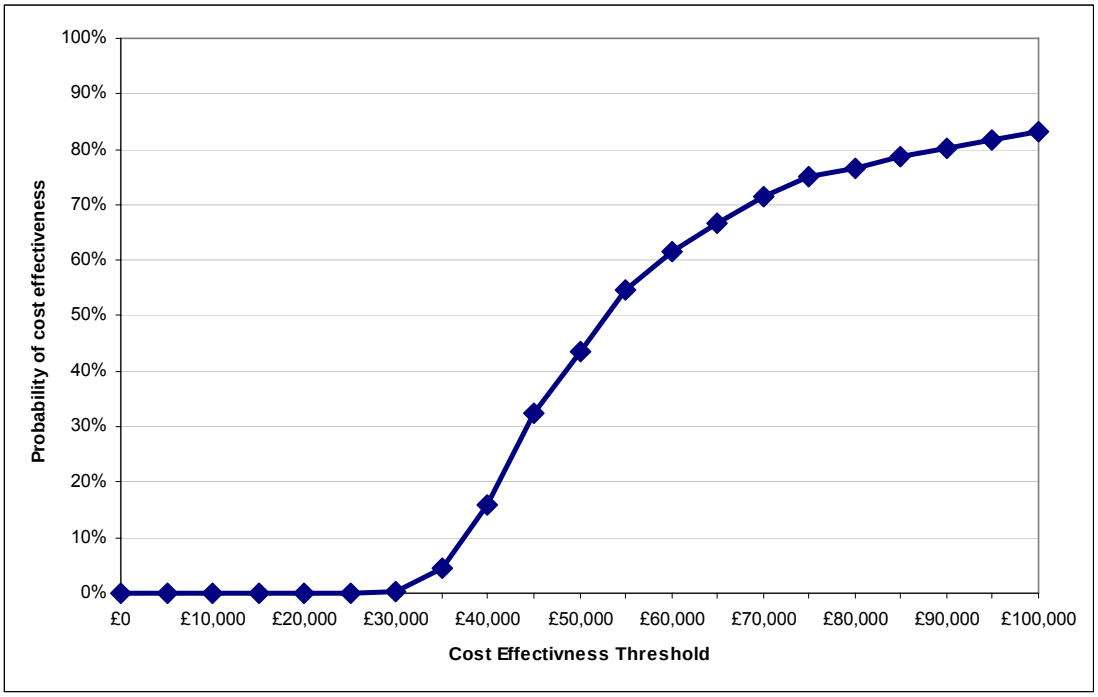


Figure 1.6. CEAC for azacitidine versus 'blended' comparators



Deterministic sensitivity analysis

Alternative vial strength/size

Celgene has made a commitment to the European Medicines Agency to pursue [redacted] and/or alternative vial strengths of azacitidine. On this basis, a supplementary economic analysis [redacted] is provided below. A sensitivity analysis was performed examining the effect of introducing [redacted] vial alongside a 100 mg vial, based on a constant cost per milligram and the azacitidine dosing in Study AZA-001. The effect of introducing this [redacted] is shown in Table 1.4.

Table 1.4. Results of sensitivity analysis of the effect of introducing [redacted] vial of azacitidine

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Pre-selected for BSC					
Azacitidine	£82,217	2.04	£54,220	1.01	£53,727
BSC	£27,998	1.03			
Pre-selected for LDC					
Azacitidine	£91,552	2.44	£55,869	1.34	£41,711
LDC	£35,684	1.10			
'Blended comparison' (that is, azacitidine versus weighted average of BSC, LDC and SDC)					
Azacitidine	£84,534	2.13	£52,189	1.09	£48,088
ALL CCR	£32,345	1.04			
NOTE: BSC = best supportive care; CCR = conventional care regimens; LDC = low-dose chemotherapy; QALY = quality-adjusted life-year; SDC = standard dose chemotherapy					

Adverse events

In the base case, adverse events (AEs) are modelled from the patient-level data from the trial, calculating the AE rate by five-week cycle. In the model, these time-dependent rates are applied while patients are on treatment. Once patients are off treatment, they assume the annualised AE rate for BSC. Two alternative scenarios are considered.

4) The annualised AE rates for azacitidine and LDC are applied in each cycle in which the patient is on treatment. Once they move off treatment, the annualised AE rate for BSC is used.
5) The annualised AE rates for azacitidine and LDC are applied to patients throughout their time in the MDS health state.

The results of these analyses are shown in Table 1.5. The results show that there is little difference between the base case and Scenario 1 for LDC, where the annualised AE rates are used during the treatment period. When the annualised AE rates are assumed to have an effect throughout the patients' time in the MDS health state, the ICER increases compared with BSC and LDC due to the increased cost in the azacitidine extended survival period. However, compared with standard-dose chemotherapy, the ICER decreases due to the high annualised AE rate in this treatment arm.

Table 1.5. Sensitivity analysis of the methodology of applying AE rates

Comparator	AE methodology scenario		
	Base case ICER	Annualised rate on treatment (1)	Annualised rate in MDS (2)
BSC	£63,177	£68,671	£69,689
LDC	£49,030	£49,213	£52,636
'Blended' comparators	£56,945	£56,945	£59,700
NOTE: AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LDC = low-dose chemotherapy; MDS = myelodysplastic syndrome			

Model using transfusion status-based utility scores

Introduction

While there is currently no widely accepted definition of 'transfusion dependence' with respect to the number and frequency of units received, estimates of the proportion of MDS patients who are transfusion dependent can be up to 80%, depending on the type of MDS and disease severity.[1]

Szende *et al* performed a study of 47 MDS patients in which transfusion independent and transfusion dependent health states were valuated using time trade-off methods to elicit utility scores. Interviews were performed on patients from centres in France, Germany, the UK and the USA. Country-specific utility values were reported.[1]

The results of this study are shown in Table 1.6 below.[1]

Table 1.6. Transfusion-based utility scores reported by Szende et al[1]

Health state	Mean utility score (standard deviation)	
	UK patients	All patients
Transfusion independent	0.85 (0.15)	0.84 (0.16)
Transfusion dependent	0.65 (0.29)	0.60 (0.28)

Method

The model developed was identical to the base case version presented under the preceding heading, except for the adjustment of utility values.

Incorporating utilities from Szende *et al*

The azacitidine clinical trial, AZA-001, reports the number of patients at baseline who are transfusion independent and transfusion dependent, and the number of patients who achieve transfusion independence during the trial. These values are used to weight the utility scores reported in Table 1.6 to achieve an average utility score for a patient in each arm of the model (see Table 1.7). Since the Szende *et al* study did not distinguish between different stages of MDS, it is assumed that the utility scores for transfusion independence and dependence remain constant throughout a patient's time in MDS. Transfusion status figures are only reported in the trial for the combined comparator arm and so are assumed to be identical for the BSC and LDC arms.

Table 1.7. Utility scores for treatment arms in the model

Health state	Proportion of patients who are TI	Weighted MDS utility score	
		All patients	UK patients
Combined comparator arm	27.9%	0.71	0.67
Azacitidine	60.3%	0.77	0.74
NOTE: MDS = myelodysplastic syndromes; TI = transfusion independent			

Results

The results of this analysis are shown in Table 1.8. The resulting ICERs are higher than the base case values; this is largely because those patients in the azacitidine arm who remain transfusion dependent do experience survival benefit compared to the standard treatments, but at the same level of utility as applied in the comparator arms. The Szende *et al* utility values only consider the patients' transfusion status and do not account for additional benefits from treatment with azacitidine (for example, avoidance of chemotherapy-related AEs, reduction in anxiety and relief from anaemia-related fatigue, even if transfusion independence has not been achieved). In some sense, therefore, these utility values are likely to represent a subset of the utility values used in the base case, except that the base case utility values may not have taken full account of transfusion status.

Table 1.8. Results of a scenario analysis using alternate utility scores

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Scenario 1: UK-based utilities Pre-selected for BSC					
Azacitidine	£91,753	2.07	£63,756	0.98	£64,892
BSC	£27,998	1.08			
Pre-selected for LDC					
Azacitidine	£101,355	2.44	£65,671	1.31	£50,018
LDC	£35,684	1.13			
'Blended comparison' (that is, azacitidine versus weighted average of BSC, LDC and SDC)					
AZA	£94,146	2.15	£61,801	1.06	£58,290
CCR	£32,345	1.09			
Scenario 2: all-country utilities Pre-selected for BSC					
Azacitidine	£91,753	2.00	£63,756	0.96	£66,092
BSC	£27,998	1.03			
Pre-selected for LDC					
Azacitidine	£101,355	2.36	£65,671	1.28	£51,117
LDC	£35,684	1.07			
'Blended comparison' (that is, azacitidine versus weighted average of BSC, LDC and SDC)					
Azacitidine	£94,146	2.08	£61,801	1.04	£59,448
BSC	£32,345	1.04			
BSC = best supportive care; CCR = conventional care regimens; LDC = low-dose chemotherapy; QALY = quality-adjusted life-year; SDC = standard-dose chemotherapy					

Conclusion

The economic analysis demonstrates that treatment of higher-risk MDS patients with azacitidine compared to LDC results in increased overall survival and quality of life gains. Cost-effectiveness analysis shows that these gains result in an ICER of £49,030 compared with LDC and £63,177 compared with BSC. Celgene believes that when the guidance for life-extending medicines is taken into consideration, treatment with azacitidine can be a cost-effective treatment option in these patients.

Incorporation of utilities from the Szende *et al* study was informative, in that it showed that a large proportion of the QALY gain associated with azacitidine probably comes from transfusion independence. Unfortunately, the data were otherwise less appropriate to use in modelling, as they did not take account of any other treatment-related differences in utility, such as other observed benefits, or adverse effects.

Section 3. Quality of life outcomes in patients with myelodysplastic syndromes

Section summary

MDS are a group of diseases characterised by ineffective haematopoiesis, which can lead to either fatal cytopenias or acute myeloid leukaemia (AML).[2] Symptoms include debilitating fatigue, infection and bleeding, which are commonly associated with anaemia, neutropenia and thrombocytopenia.[3-5] MDS treatment involves improving patient survival and quality of life (QoL) while decreasing the likelihood of progression to AML.[6] The only potential cure is haematopoietic stem cell transplantation, although several alternative treatments now show great promise.[7] As the majority of patients with MDS are anaemic,[3] many rely on red blood cell (RBC) transfusions (transfusion dependence). Transfusion independence has been associated with a positive impact on health-related QoL (HRQoL)[8] and an increase in the likelihood of survival,[9] and has therefore become a main aim of treatment management. This report summarises QoL data from the MDS UK patient group, highlighting the important issues both from a patient and clinical outcome point.

Quality of life of patients with MDS

Despite the clinical importance of QoL in patients with MDS, there are few data on the relationship between MDS-associated symptoms and specific MDS features.

In collaboration with the Mayo Clinic and the MDS Foundation, an internet-based survey of QoL in patients with MDS was therefore carried out to better understand the burden of disease-associated symptoms in a large cohort of patients with MDS.[10] This 120-question survey collected information on patient demographics, recent blood counts and disease specifics, and incorporated validated QoL instruments and questions about specific therapies. The main part of the survey comprised questions designed to assess the patients' QoL and the lifestyle effects of symptoms, such as fatigue. QoL instruments included the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) Scale;[11] the Brief Fatigue Inventory (BFI);[12] the Charlson Co-Morbidity Index (CCI);[13] and the Godin Leisure Time Activity Score (LAS).[14]

The 359 survey respondents were typical of MDS patients in terms of demographics, blood counts and disease subtypes. Their mean age was 63.5 years (range: 20–90), 56% were male and their diagnoses spanned the MDS spectrum, with 33% reported as unclassifiable/subtype unknown. The most recent haemoglobin level was ≤12.0 g/dl in 85% of respondents and ≤10.0 g/dl in 60% (median: 9.9 g/dl). However, these values may have reflected transfused values, as 65% of patients reported having received blood products at some time since MDS diagnosis. Severe thrombocytopenia was less frequent than neutropenia.[10]

The most common symptom endorsed by patients with MDS was excessive fatigue (89%), followed by bruising/bleeding (55%). Regarding patients' ability to work, only 27% were working outside the home, 60% were retired of which only 4.6% were ≤62 years old, suggesting that MDS is not a common cause of early retirement.[10]

Erythropoiesis-stimulating agents (ESAs) were the most common (55%) drug therapies previously or currently used, followed by azacitidine (19%) and corticosteroids (16%). Fatigue was strongly associated with ESA use, with the majority of patients with fatigue (95%) reporting ESA use. The rate of fatigue in those who did not use ESAs was 82% ($p=0.0001$ in comparison of fatigue rates by ESA use), suggesting that these agents are commonly prescribed by clinicians despite their severe side-effects. Bone pain (48% of ESA users versus 28% of ESA non-users; $p=0.001$) and skin rash (30% of ESA users versus 18% of ESA non-users; $p=0.005$) were also strongly associated with the use of ESAs, consistent with the known adverse event profile of these agents.[10]

Normalised scores on the QoL instruments were markedly worse for patients than for the general population. On the FACT-An scale, patients with MDS scored a mean of 50.5, compared with a mean of 77.1 scored by healthy controls (where 100 is best possible QoL; $p<0.0001$) (see Table 2.1). Similarly for the BFI measurement, respondents with MDS had a mean score of 5.8 versus 2.2 for healthy controls (scale of 0–10, where 0 is the best possible result; $p<0.0001$). Patients reported a mean of 1.5 co-morbidities on the CCI and a LAS of 19.7 (higher scores are better; a score of 24 is the basic public health recommendation).[10]

Table 2.1. Quality of life scoring summary – MDS versus healthy population[10]

Brief Fatigue Inventory Overall Score	n=320
Mean score (SD)	5.8 (2.58)
Mean score for healthy controls	2.2
Charlson Co-Morbidity Index-Total	n=359
Mean number of co-morbidities (SD)	1.5 (2.18)
Charlson Co-Morbidity Index- Score	
0	141 (39.3%)
1 or 2	141 (39.3%)
3 or 4	50 (13.9%)
≥5	27 (7.5%)
FACT-An Total Score	n=345
Mean (SD)	50.5 (20.89)
Mean score for healthy controls	77.1
FACT-An Fatigue Subscale Score	n=346
Mean (SD)	46.1 (24.6)
FACT-An Non-Fatigue Subscale Score	n=346
Mean (SD)	58.4 (17.8)
Godin Leisure-Time Activity Score	n=320
Mean score (SD)	19.7 (73.01)

NOTE: FACT-An = Functional Assessment of Cancer Therapy-Anaemia; SD = standard deviation

Patient fatigue was associated with significant impairment of both HRQoL and ability to work and participate in desired activities. However, in the logistic regression modelling, self-perceived fatigue and BFI/FACT-An scores did not correlate with haemoglobin levels (Spearman correlation coefficients: –0.045 [p=0.48] for BFI score; –0.037 [p=0.54] for FACT-An fatigue subscale; and 0.21 [p=0.73] for self-perceived fatigue over the past two weeks). There was also no statistical correlation between ever requiring a transfusion and BFI/FACT-An scores, suggesting that fatigue can arise in MDS for other reasons than anaemia alone. However, contrasting findings from a 50-patient QoL analysis of MDS patients, which showed a strong correlation between fatigue/QoL and haemoglobin level, would seem to suggest that alleviation of RBC deficiency would probably be associated with some relief from fatigue, although perhaps not complete relief.[10,15]

These survey results, particularly the prevalence of fatigue, highlight the high symptom burden experienced by patients with MDS. They also suggest that currently available MDS treatments inadequately ameliorate common MDS-associated symptoms and, in fact, contribute to a decrement in the already compromised QoL of a patient.

Understanding the impact of MDS at all levels is important to address the specific needs of patients, and the clinical consequences of the disease and its treatments. From 2004 to 2007, the MDS Foundation convened 29 MDS forums run by clinical nurse specialists for patients and their families and caregivers to discuss QoL issues.[5] Forums included open dialogue, question-and-answer sessions and anonymous questionnaires to assess patients' knowledge about their disease, feelings about relationships with their physicians, perceptions of attitude and support by healthcare providers, and the effect of management or treatment strategies on QoL.[5]

These forums revealed that the burden of MDS and its management has wide-ranging effects on patients' lives. Feelings of fear, anxiety, anger, frustration, loneliness, depression and helplessness were expressed, especially by younger adult patients. Specifically, fatigue frequently and significantly affected QoL, impacting on participation in social and family life and the ability to perform activities of daily living — 25% reported it 'takes an effort to engage in normal activities'; 16% reported they cannot perform active work; and an additional 9% reported they require 'occasional' or 'considerable' assistance. Although the vast majority of patients looked forward to the remainder of their lives, they said that their world changed forever when diagnosed with MDS. They stated that the disease had forced them to give up things that make life worth living and that they were now too tired to participate in such activities.[5]

Disease management was time consuming, and included receiving diagnostic testing, blood transfusions and treatment, with eight hours a week for blood transfusions quoted by one patient. Three-quarters of respondents reported needing transfusions, with most patients requiring repeated RBC and/or platelet transfusions. Transfusions were considered 'a necessary evil' to cope with fatigue. Second to fatigue, repeated RBC transfusions with iron chelation therapy had a significant negative impact on QoL. The majority of patients also reported the use of antibiotics.[5]

There is little structured, published information on the value of transfusion independence compared with transfusion dependence to patients with MDS. Facilitated by the MDS Foundation, a study was therefore carried out to evaluate how MDS patients value transfusion-independent living compared with transfusion-dependent living, using a validated health utility assessment.[1]

In 2005–06, health utility interviews with 47 patients with MDS in France, Germany, the UK and the USA were undertaken to elicit the value of transfusion independence or reduced transfusion burden compared with transfusion dependence. Health states were developed, based on literature and patient forum discussions, and were validated by a leading clinical expert in the diagnosis and treatment of MDS. Each health state card included different levels of severity/intensity of problems on specific aspects of HRQoL, including: reliance on blood transfusions and healthcare provider facility; the need to arrange one's life around medical appointments; fatigue and tiredness that limits performance of routine physical activities; interference of disease with social and family life; worry about the future due to health condition; discomfort associated with medical conditions and treatment; feeling of being at risk of infection; reliance on support persons for self-care and routine activities; feelings of being a burden to family; and feeling sad, hopeless and helpless.[1]

Patients (45% male) had a mean age of 67 years (range: 29–83). The majority were retired (70%) and lived with family, a partner or spouse, or friends (79%). The mean time from MDS diagnosis was five years (range: 1–23). Most patients (87%) had received previous transfusions, and 49% had received a transfusion in the last three months. HRQoL was assessed using the EuroQol EQ-5D questionnaire.[1,16] A mean EQ-5D index score (where 'full health' has a value of 1 and 'dead' a value of 0) of 0.78 was reported, with patients reporting at least some problem with mobility (45%), usual activities (40%), pain/discomfort (47%) and anxiety/depression (34%).[1]

The feeling thermometer visual analogue scale (VAS) and the time trade-off (TTO) methods were used in the face-to-face interviews to value the health states on a 0 (dead) to 1 (perfect health) scale.[1,17-19] Patients rated their own health as 0.62 with the VAS method and 0.86 with the TTO method on the 'dead/perfect health' scale. Few patients had difficulty understanding the VAS (n=3) and TTO (n=4) exercises. Paired t-tests showed that mean (± standard deviation [SD]) VAS scores were significantly better for the transfusion independent state compared with health states with reduced transfusion requirements (78 ± 15 versus 56 ± 16; $p<0.001$) and transfusion dependence (78 ± 15 versus 31 ± 18; $p<0.001$). The Wilcoxon signed-rank test showed that mean (± SD) TTO scores for transfusion independence were significantly better than for reduced

transfusion (0.84 ± 0.16 versus 0.77 ± 0.21; p<0.001) or transfusion dependence (0.84 ± 0.16 versus 0.60 ± 0.28; p<0.001). Three patients rated transfusion dependence as worse than being dead. Similar results were observed across countries.[1]

The results from this study provide evidence that transfusion independence is associated with better HRQoL scores. Patients put a high value on being transfusion free when their preferences were measured on a utility scale, indicating that they are willing to trade off length of life to achieve transfusion independence. Patients who were transfusion dependent were willing to make the most substantial sacrifices, as reflected by the 0.60 utility score. The findings of this study suggest an important role for new treatments aimed at achieving greater transfusion independence for patients with MDS.[1]

Conclusion

Patients with MDS have multiple issues, such as advancing age, comorbid conditions, fatigue, infection, bleeding and treatment-related complications, all of which adversely impact their QoL. Due to this high symptom burden, MDS patients place great value on achieving transfusion independence, which, to an extent, gives them back control over their activities, outlook and relationships. This priority is reflected in the utility study results. These surveys highlight the need for treatments that allow patients to achieve the level of independence that they desire, in addition to improving their overall outcomes.[15]

Section 4. Literature review: patient preference trials

Section summary

This section involves a literature review describing the main concerns facing “patient preference” trials. The trials mentioned in this review have limited relevance to the pivotal azacitidine trial, AZA-001, as they all involve patients in the actual assignment of control/active treatment. In AZA-001 the allocation of patients to active or control treatment was randomised, but clinical judgment and patient preference played a combined role in determining which control treatment patients were pre-allocated to.

Introduction

Generally, literature searches revealed studies focusing on (1) treatment preferences, (2) factors that influence patient choice, (3) patient preference to participate in shared decision making, and (4) influence of treatment preference and patient expectation in health outcomes. Studies collected information using surveys, questionnaires, and evaluation instruments within a clinical trial setting, e.g. patients were asked to give reasons for preferring one therapy over another or rate their treatment satisfaction. They were carried out in a wide range of indications, including cancer. The majority of these studies did not address the question of the influence of patient preference; the following accounts contain information that may be considered relevant to this issue.

Methods

PubMed literature searches were carried out using search terms relevant to patient preference trials and the extent to which patient preference influences the treatment decision/allocation to treatment in clinical trials (Table 3.1). Abstracts and full articles in the English language were reviewed based on the appropriateness of their title. Additionally, the first 20 hits of a Google search on ‘to what extent does patient preference influence the decision about treatment’ were assessed and, where appropriate, reviewed.

Table 3.1. PubMed search terms and number of 'hits'

Search terms	No. of hits	Date range
"To what extent does patient preference influence the decision about treatment" (Google)	8	2010 - 1999
Patient preference AND treatment decision	936	2010 – 1951
Patient preference AND influence and treatment	336	2010 – 1982
Chemotherapy AND preference AND patient influence	146	2010 – 1983
Patient preference AND influence AND chemotherapy	107	2010 – 1983
Patient preference trials	881	2010 – 1966

Results

There are general concerns that randomisation procedures undermine the validity of clinical trials because it ignores patients' treatment preferences. Randomised controlled trials (RCTs) disregard patient choice. It is therefore important to know the extent of any preference effects to evaluate RCT findings.[20] It is argued that until preference effects on the effectiveness of treatment are better understood, unblinded randomised studies do not necessarily provide reliable information about the effects of treatment.[20] The following account reviews patient preference trials and whether the validity of clinical trials may be influenced by the preferences of the participants about their treatment.

A discussion regarding patient preference trials highlights the problems encountered by open-label RCTs.[21,22] Such problems include when patients have such strong treatment preferences that they refuse randomisation (which restricts generalisation of the results, as participants may not be representative) or when patients with strong treatment preferences are randomised but not to their treatment choice (which may result in patient demoralisation or poor adherence to treatment).[22] These situations may result in a treatment effect associated with patient preference rather than with therapeutic efficacy. Patient preference trials, where patients with treatment preferences are allowed their treatment choice and those who do not have a strong preference are randomised to treatment, may overcome this problem. However, comparisons between randomised and non-randomised group are unreliable because of unknown and uncontrolled confounders. One alternative approach is to determine the strength and direction of patient preferences before randomisation, and randomise all consenting patients. This method has the advantages of a fully randomised design and allows assessment of the

preference-outcome interaction.[22] Another approach is to randomly assign patients to either a preference trial (subjects choose their treatment) or to a randomised trial (random allocation to treatment).[23] Between-trial comparisons can then be used to determine the influence of preference on outcome.

Patient preference designs may be considered to complement RCTs rather than to replace them.[22] The effect of patient preference for a treatment within an open-label study has been shown to both have no effect on treatment outcomes and to influence treatment outcomes. The following focuses more on reviews of patient preference trials rather than on individual studies.

A study with a non-patient sample comparing a randomised arm to a preference arm found that there was no effect of choice.[24] While participants mismatched to preference felt less positive, this did not affect belief in treatment, adherence, or engagement. King and colleagues conducted a systematic review of 32 trials, and then 34 trials, measuring or recording patient or physician preference, including allocation of participants to random and preference cohorts.[25,26] Although treatment preferences were found to affect trial recruitment, there was less evidence of bias in the characteristics of patients agreeing to randomisation. Differences in outcome across the trials between randomised and preference groups were generally small, particularly in large trials and after accounting for baseline differences. Preferences did not affect attrition. This review concluded that there was little evidence that preferences substantially interfere with trial outcomes, although they were found to influence whether patients participate in randomised trials. Findings were considered to support the use of observational methods when preferences based on informed expectations or strong ethical objections to an RCT exist.

More studies demonstrated an effect of patient preference. A meta-analytic review aiming to determine whether including patient preferences has an effect on treatment outcome, summarised data from over 2,300 patients across 26 studies comparing the treatment outcome differences between patients matched to a preferred treatment and patients not matched to a preferred treatment.[27] Findings indicated that there was a small significant effect in favour of treatment preference. Matched clients had a 58%

chance of showing greater improvement, and were about half as likely to dropout of treatment compared with patients not receiving a preferred treatment.

The Preference Collaborative Review Group[28] systematically reviewed fully randomised patient preference trials to explore the impact of preferences on attrition and outcome by meta-analysis of patient level data. Data for the 8 musculoskeletal trials (n=1594) were combined, and three groups were compared: patients who had a preference and were randomly allocated to their preferred treatment; patients who had a preference and were randomly allocated to the treatment they did not prefer; and patients who had no preference. Patients who were randomised to their preferred treatment had a standardised effect size greater than that of those who had no preference (effect size 0.162; p=0.04). They also did better than participants who did not receive their preferred treatment (effect size 0.152), although this was not statistically significant (p=0.11). Participants allocated to their undesired treatment had similar outcomes to those who had no preference, although they were less likely to be lost to first follow-up. There was no difference in attrition between patients allocated to their preference and those who were indifferent. The group concluded that preferences among patients in musculoskeletal trials are associated with treatment effects, and that preferences should be ascertained before randomisation in open-label randomised trials.

The aim of a systematic review of partially randomised acupuncture trials was to determine whether random participant assignment caused fewer benefits to the participants.[29] Six trials with adequate randomisation generation and concealment of participant group allocation, and samples large enough to satisfy a power calculation, found that patients who were randomly assigned to treatment groups had fewer health benefits than those who were non-randomly assigned. The two groups had different demographics and health outcomes, substantial numbers of patients refused randomisation, while significantly more dropped out from the observational group than the randomised group.

A study examining how initial treatment preferences of participants in a shoulder pain trial affected functional outcome and future treatment preferences showed that preferences prior to treatment can affect outcome.[30] However, irrespective of pre-randomisation preference and whether the preferred treatment was received, treatment

outcome (six months post-randomisation) had a stronger influence on post-treatment preferences.

The extent to which patient preference influences the treatment decision/allocation to treatment

For completeness, the following account approaches patient preference and their influence over the treatment decision from a different angle. Little information was found relating directly to this issue.

A review of decision-making and quality of life in the treatment of cancer reported that when considering how to treat patients, physicians prioritise factors such as stage of disease, patient age and comorbid illnesses.[31] These apparently are balanced with, among other factors, patient's preferences, which physicians are often unable to effectively judge. An earlier review of patients' needs and preferences in advanced colorectal cancer reported that the most important factor in clinical decision-making was the patient's own preference.[32] Patients were frequently not consulted regarding their treatment, although it was considered to be impossible to make decisions about what is best for patients without involving them in the decision-making process.

Findings of a postal survey indicated that patient expectations and practice characteristics can influence physicians.[33] Canadian family physicians were strongly influenced by a patient demanding/requesting a screening or diagnostic test, but were not influenced in the treatment scenario (prescribing antibiotics for acute bronchitis) where hours and type of practice were significant. However, a survey of 778 French general practitioners (GP) revealed that patient characteristics largely explain the prescription (antibiotics for acute rhinopharyngitis), even if GP or practice setting characteristics and environmental factors also exert considerable influence.[34]

A methodology paper attempts to provide conceptual clarity about shared treatment decision-making, focusing on potentially life threatening illnesses where important decisions have to be made during the disease process and several treatment options exist with different possible outcomes.[35]

Conclusion

The most reliable information about treatment effects comes from RCTs.[36] However, if patient preferences can influence the effectiveness of treatments, then RCTs (particularly open-label studies) may incorrectly attribute effects to a treatment's properties only. Due to the uncertainty of the preference-treatment interaction, data from both RCTs and patient preference trials should form the evidence base of treatment effectiveness.

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Appendices

Appendix 1. Haematologist survey

The following questions relate to the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- intermediate2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10–29 % marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20–30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification.

Please answer all of the following questions with regard to this population.

Q1 Of the patients you have treated in the **past three years**, to approximately what number of them did you assign the following care optionsX Please give a number

If you changed the treatment of any patients during a year, please consider the last treatment you assigned them.

Year	Supportive care alone	Supportive care plus low-dose cytarabine arabinoside (Ara-C)	Supportive care plus standard-dose chemotherapy	Azacitidine (Vidaza)	Other
2008					
2009					
2010					

Q2 Please review the following list of the clinical criteria which may be used in selecting patients to receive low-dose Ara-C, and indicate how likely each of these characteristics would lead you to decide that a patient is **clinically suitable** for low-dose Ara-C rather than supportive care or standard dose chemotherapy.

| 5 = Very likely | 4 = Likely | 3 = Neither likely nor unlikely | 2 = Unlikely | 1= Very unlikely |

Comorbidities

Pulmonary impairment (moderate to severe)

Cardiac disease (Ischaemic or valvular)

Hepatic impairment

Renal impairment

Diabetes

Obesity

Rheumatoid arthritis or osteoarthritiss

Prior infections

Symptom control

Symptomatic cytopenias (any)

Transfusion dependence

Disease classification (FAB)

RAEB

RAEB-T

CMML

AML

IPSS score

Int-1

Int-2

High

Karyotype risk / cytogenetics

Good

Intermediate

Poor

ECOG performance status

0

1

2

Q3 When you assess whether a patient would be clinically suitable for low-dose Ara-C, what percentage of patients would you consider to have clinical characteristics which are **appropriate** for receiving low-dose Ara-CX Please give a percentage

_ _ _ %

Q4 When you assess whether a patient would be clinically suitable for low-dose Ara-C, what percentage of patients would you consider to have clinical characteristics which are **inappropriate** for receiving low-dose Ara-CX Please give a percentage

_ _ _ %

Q5 Of the patients whom you have assessed as clinically suitable for treatment with low-dose Ara-C, approximately what percentage of these patients would you consider to have clinical characteristics which are **borderline** with respect to suitability for low-dose Ara-CX Please give a percentage

_ _ _ %

Q6 For each of the following scenarios please indicate, using percentages, the frequency with which your decision to treat with low-dose Ara-C was shaped by patient preference. Please give a percentage

If Vidaza *(5-azacitidine)* has significantly changed the way you make decisions, please consider how you made decisions before the product was available.

Clinical suitability for low-dose Ara-C.	**Low-dose Ara-C given, accounting for patient preference**
Suitable	- - -%
Borderline	- - -%
Not clinically suitable	- - -%

Q7 For each of the following scenarios please indicate, using percentages, the frequency with which your decision not to treat with low-dose Ara-C was shaped by patient preference. Please give a percentage

If Vidaza *(5-azacitidine)* has significantly changed the way you make decisions, please consider how you made decisions before the product was available.

Clinical suitability for low-dose Ara-C	**Low-dose Ara-C not given, accounting for patient preference**
Suitable	- - -%
Borderline	- - -%
Not clinically suitable	- - -%

Appendix 2. Haematologist survey detailed results

Fieldwork dates: 11 August – 31 August 2010

Sample: 72 UK-based Haematologists

Q1 Of the patients you have treated in the past three years, to approximately what number of them did you assign the following care optionsX Please give a number		
	Total	
(Summary of coding)	N	%
2008 (Supportive care alone)		
0	3	4%
1-5	26	36%
6-10	20	28%
11-15	6	8%
16-20	8	11%
21-25	1	1%
26-30	5	7%
31+	3	4%
Mean	12	
Base	72	
2008 (Supportive care plus low-dose cytarabine arabinoside (Ara-C))		
0	17	24%
1	5	7%
2	13	18%
3	13	18%
4	4	6%
5	6	8%
6	2	3%
7	1	1%
8	1	1%
10	5	7%
11+	5	7%
Mean	4	
Base	72	

[Q1 continued]

2008 (Supportive care plus standard-dose chemotherapy)		
0	12	17%
1	10	14%
2	10	14%
3	7	10%
4	7	10%
5	7	10%
6	3	4%
7	2	3%
8	1	1%
10	5	7%
15	3	4%
16+	5	7%
Mean	6	
Base	72	
2008 (Azacitidine (Vidaza))		
0	56	78%
1	5	7%
2	6	8%
3	1	1%
4	1	1%
6	1	1%
8	1	1%
10	1	1%
Mean	1	
Base	72	
2008 (Other)		
0	59	82%
1	4	6%
2	3	4%
3	1	1%
5	2	3%
10	2	3%
20	1	1%
Mean	1	
Base	72	

[Q1 continued]

2009 (Supportive care alone)		
0	3	4%
1-5	27	38%
6-10	14	19%
11-15	17	24%
16-20	6	8%
21-25	1	1%
26-30	1	1%
31+	3	4%
Mean	11	
Base	72	
2009 (Supportive care plus low-dose cytarabine arabinoside (Ara-C))		
0	17	24%
1	9	13%
2	9	13%
3	13	18%
4	3	4%
5	6	8%
6	3	4%
7	2	3%
8	1	1%
10	4	6%
14	1	1%
15+	4	6%
Mean	4	
Base	72	

[Q1 continued]

2009 (Supportive care plus standard-dose chemotherapy)		
0	10	14%
1	8	11%
2	10	14%
3	9	13%
4	7	10%
5	6	8%
6	1	1%
7	1	1%
8	3	4%
10	7	10%
12	1	1%
15	2	3%
16	1	1%
18	1	1%
20	2	3%
21+	3	4%
Mean	7	
Base	72	
2009 (Azacitidine (Vidaza))		
0	38	53%
1	13	18%
2	10	14%
3	4	6%
4	1	1%
5	2	3%
7	2	3%
10	1	1%
15	1	1%
Mean	1	
Base	72	

[Q1 continued]

2009 (Other)		
0	58	81%
1	6	8%
2	2	3%
3	1	1%
5	1	1%
10	1	1%
15	2	3%
20	1	1%
Mean	1	
Base	72	
2010 (Supportive care alone)		
0	2	3%
1-5	35	49%
6-10	15	21%
11-15	8	11%
16-20	5	7%
21-25	2	3%
26-30	1	1%
31+	4	6%
Mean	10	
Base	72	
2010 (Supportive care plus low-dose cytarabine arabinoside (Ara-C))		
0	21	29%
1	11	15%
2	12	17%
3	6	8%
4	3	4%
5	4	6%
6	4	6%
7	2	3%
8	2	3%
10	2	3%
12	1	1%
19	1	1%
20	2	3%
30	1	1%
Mean	4	
Base	72	

[Q1 continued]

2010 (Supportive care plus standard-dose chemotherapy)		
0	15	21%
1	6	8%
2	12	17%
3	6	8%
4	5	7%
5	5	7%
6	3	4%
7	4	6%
8	1	1%
10	6	8%
12	1	1%
15	2	3%
16+	6	8%
Mean	6	
Base	72	
2010 (Azacitidine (Vidaza))		
0	42	58%
1	9	13%
2	8	11%
3	7	10%
4	3	4%
5	1	1%
15	1	1%
20	1	1%
Mean	1	
Base	72	

2010 (Other)		
0	58	81%
1	5	7%
2	2	3%
3	1	1%
4	1	1%
5	1	1%
6	1	1%
7	1	1%
15	1	1%
20	1	
Mean	1	
Base	72	

Q1 Of the patients you have treated in the past three years, to approximately what number of them did you assign the following care optionsX Please give a number (Summary of means)	
Care option	Mean number of patients
2008 (Supportive care alone)	12
2008 (Supportive care plus low-dose cytarabine arabinoside (Ara-C))	4
2008 (Supportive care plus standard-dose chemotherapy)	6
2008 (Azacitidine (Vidaza))	1
2008 (Other)	1
2009 (Supportive care alone)	11
2009 (Supportive care plus low-dose cytarabine arabinoside (Ara-C))	4
2009 (Supportive care plus standard-dose chemotherapy)	7
2009 (Azacitidine (Vidaza))	1
2009 (Other)	1
2010 (Supportive care alone)	10
2010 (Supportive care plus low-dose cytarabine arabinoside (Ara-C))	4
2010 (Supportive care plus standard-dose chemotherapy)	6
2010 (Azacitidine (Vidaza))	1
2010 (Other)	1

Q2 Please review the following list of the clinical criteria which may be used in selecting patients to receive low-dose Ara-C, and indicate how likely each of these characteristics would lead you to decide that a patient is clinically suitable for low-dose Ara-C rather than supportive care or standard dose chemotherapy.		
	Total	
	N	%
Co-morbidities		
Pulmonary impairment (moderate to severe)		
1= Very unlikely	4	6%
2 = Unlikely	17	24%
3 = Neither likely nor unlikely	27	38%
4 = Likely	18	25%
5 = Very likely	6	8%
Mean	3.1	
Base	72	
Cardiac disease (Ischaemic or valvular)		
1= Very unlikely	3	4%
2 = Unlikely	16	22%
3 = Neither likely nor unlikely	20	28%
4 = Likely	26	36%
5 = Very likely	7	10%
Mean	3.3	
Base	72	
Hepatic impairment		
1= Very unlikely	3	4%
2 = Unlikely	21	29%
3 = Neither likely nor unlikely	25	35%
4 = Likely	20	28%
5 = Very likely	3	4%
Mean	3	
Base	72	
Renal impairment		
1= Very unlikely	3	4%
2 = Unlikely	16	22%
3 = Neither likely nor unlikely	24	33%
4 = Likely	27	38%
5 = Very likely	2	3%
Mean	3.1	
Base	72	

[Q2 continued]

Diabetes		
1= Very unlikely	2	3%
2 = Unlikely	15	21%
3 = Neither likely nor unlikely	41	57%
4 = Likely	11	15%
5 = Very likely	3	4%
Mean	3	
Base	72	
Obesity		
1= Very unlikely	2	3%
2 = Unlikely	16	22%
3 = Neither likely nor unlikely	43	60%
4 = Likely	9	13%
5 = Very likely	2	3%
Mean	3	
Base	72	
Rheumatoid arthritis or osteoarthritis		
1= Very unlikely	3	4%
2 = Unlikely	17	24%
3 = Neither likely nor unlikely	42	58%
4 = Likely	9	13%
5 = Very likely	1	1%
Mean	2.8	
Base	72	
Prior infections		
1= Very unlikely	1	1%
2 = Unlikely	15	21%
3 = Neither likely nor unlikely	37	51%
4 = Likely	19	26%
5 = Very likely	0	0%
Mean	3	
Base	72	

[Q2 continued]

Symptom control		
Symptomatic cytopenias (any)		
1= Very unlikely	2	3%
2 = Unlikely	11	15%
3 = Neither likely nor unlikely	25	35%
4 = Likely	27	38%
5 = Very likely	7	10%
Mean	3.4	
Base	72	
Transfusion dependence		
1= Very unlikely	2	3%
2 = Unlikely	10	14%
3 = Neither likely nor unlikely	26	36%
4 = Likely	28	39%
5 = Very likely	6	8%
Mean	3.4	
Base	72	
Disease classification (FAB)		
RAEB		
1= Very unlikely	2	3%
2 = Unlikely	16	22%
3 = Neither likely nor unlikely	24	33%
4 = Likely	26	36%
5 = Very likely	4	6%
Mean	3.2	
Base	72	
RAEB-T		
1= Very unlikely	2	3%
2 = Unlikely	17	24%
3 = Neither likely nor unlikely	24	33%
4 = Likely	20	28%
5 = Very likely	9	13%
Mean	3.2	
Base	72	

[Q2 continued]

CMML		
1= Very unlikely	6	8%
2 = Unlikely	30	42%
3 = Neither likely nor unlikely	21	29%
4 = Likely	15	21%
5 = Very likely	0	0%
Mean	2.6	
Base	72	
AML		
1= Very unlikely	5	7%
2 = Unlikely	14	19%
3 = Neither likely nor unlikely	17	24%
4 = Likely	24	33%
5 = Very likely	12	17%
Mean	3.3	
Base	72	
IPSS score		
Int-1		
1= Very unlikely	8	11%
2 = Unlikely	23	32%
3 = Neither likely nor unlikely	21	29%
4 = Likely	19	26%
5 = Very likely	1	1%
Mean	2.8	
Base	72	
Int-2		
1= Very unlikely	4	6%
2 = Unlikely	16	22%
3 = Neither likely nor unlikely	27	38%
4 = Likely	22	31%
5 = Very likely	3	4%
Mean	3.1	
Base	72	

[Q2 continued]

High		
1= Very unlikely	7	10%
2 = Unlikely	15	21%
3 = Neither likely nor unlikely	21	29%
4 = Likely	19	26%
5 = Very likely	10	14%
Mean	3.1	
Base	72	
Karyotype risk / cytogenics		
Good		
1= Very unlikely	2	3%
2 = Unlikely	15	21%
3 = Neither likely nor unlikely	23	32%
4 = Likely	27	38%
5 = Very likely	5	7%
Mean	3.3	
Base	72	
Intermediate		
1= Very unlikely	1	1%
2 = Unlikely	12	17%
3 = Neither likely nor unlikely	38	53%
4 = Likely	19	26%
5 = Very likely	2	3%
Mean	3.1	
Base	72	
Poor		
1= Very unlikely	7	10%
2 = Unlikely	28	39%
3 = Neither likely nor unlikely	22	31%
4 = Likely	12	17%
5 = Very likely	3	4%
Mean	2.7	
Base	72	

[Q2 continued]

ECOG performance status		
0		
1= Very unlikely	4	6%
2 = Unlikely	21	29%
3 = Neither likely nor unlikely	22	31%
4 = Likely	17	24%
5 = Very likely	8	11%
Mean	3.1	
Base	72	
1		
1= Very unlikely	2	3%
2 = Unlikely	11	15%
3 = Neither likely nor unlikely	33	46%
4 = Likely	22	31%
5 = Very likely	4	6%
Mean	3.2	
Base	72	
2		
1= Very unlikely	5	7%
2 = Unlikely	16	22%
3 = Neither likely nor unlikely	22	31%
4 = Likely	24	33%
5 = Very likely	5	7%
Mean	3.1	
Base	72	

Q2 Please review the following list of the clinical criteria which may be used in selecting patients to receive low-dose Ara-C, and indicate how likely each of these characteristics would lead you to decide that a patient is clinically suitable for low-dose Ara-C rather than supportive care or standard dose chemotherapy. (Summary of means)	
Criteria	Mean likeliness out of 5
Co-morbidities	
Pulmonary impairment (moderate to severe)	3.1
Cardiac disease (Ischaemic or valvular)	3.3
Hepatic impairment	3
Renal impairment	3.1
Diabetes	3
Obesity	3
Rheumatoid arthritis or osteoarthritis	2.8
Prior infections	3
Symptom control	
Symptomatic cytopenias (any)	3.4
Transfusion dependence	3.4
Disease classification (FAB)	
RAEB	3.2
RAEB-T	3.2
CMML	2.6
AML	3.3
IPSS score	
Int-1	2.8
Int-2	3.1
High	3.1
Karyotype risk / cytogenics	
Good	3.3
Intermediate	3.1
Poor	2.7
ECOG performance status	
0	3.1
1	3.2
2	3.1

Q3 When you assess whether a patient would be clinically suitable for low-dose Ara-C, what percentage of patients would you consider to have clinical characteristics which are appropriate for receiving low-dose Ara-CX Please give a percentage		
	Total	
(Summary of coding)	N	%
0%	4	6%
1-10%	6	8%
11-20%	11	15%
21-30%	14	19%
31-40%	12	17%
41-50%	11	15%
51-60%	7	10%
61-70%	3	4%
71-80%	2	3%
81-90%	2	3%
91-99%	0	0%
100%	0	0%
Mean	36%	
Base	72	

Q4 When you assess whether a patient would be clinically suitable for low-dose Ara-C, what percentage of patients would you consider to have clinical characteristics which are inappropriate for receiving low-dose Ara-CX Please give a percentage		
	Total	
(Summary of coding)	N	%
0%	1	1%
1-10%	2	3%
11-20%	4	6%
21-30%	13	18%
31-40%	15	21%
41-50%	15	21%
51-60%	7	10%
61-70%	4	6%
71-80%	6	8%
81-90%	2	3%
91-99%	2	3%
100%	1	1%
Mean	48%	
Base	72	

Q5 Of the patients for whom you have assessed as clinically suitable for treatment with low-dose Ara-C, approximately what percentage of these patients would you consider to have clinical characteristics which are borderline with respect to suitability for low-dose Ara-CX Please give a percentage		
	Total	
(Summary of coding)	N	%
0%	6	8%
1-10%	17	24%
11-20%	20	28%
21-30%	13	18%
31-40%	4	6%
41-50%	11	15%
51-60%	0	0%
61-70%	0	0%
71-80%	1	1%
81-90%	0	0%
91-99%	0	0%
100%	0	0%
Mean	23%	
Base	72	

Q6 For each of the following scenarios please indicate, using percentages, the frequency with which your decision to treat with low-dose Ara-C was shaped by patient preference. Please give a percentage If Vidaza (5-azacitidine) has significantly changed the way you make decisions, please consider how you made decisions before the product was available.		
	Total	
(Summary of coding)	N	%
Suitable for low-dose Ara-C (Low-dose Ara-C given, accounting for patient preference)		
0%	5	7%
1-10%	7	10%
11-20%	9	13%
21-30%	8	11%
31-40%	8	11%
41-50%	12	17%
51-60%	3	4%
61-70%	7	10%
71-80%	4	6%
81-90%	3	4%
91-99%	1	1%
100%	5	7%
Mean	44%	
Base	72	
Borderline for low-dose Ara-C (Low-dose Ara-C given, accounting for patient preference)		
0%	7	10%
1-10%	14	19%
11-20%	7	10%
21-30%	8	11%
31-40%	6	8%
41-50%	18	25%
51-60%	3	4%
61-70%	2	3%
71-80%	2	3%
81-90%	1	1%
91-99%	0	0%
100%	4	6%
Mean	36%	
Base	72	

[Q6 continued]

Unsuitable for low-dose Ara-C (Low-dose Ara-C given, accounting for patient preference)		
0%	21	29%
1-10%	12	17%
11-20%	8	11%
21-30%	7	10%
31-40%	6	8%
41-50%	7	10%
51-60%	3	4%
61-70%	2	3%
71-80%	2	3%
81-90%	0	0%
91-99%	2	3%
100%	2	3%
Mean	26%	
Base	72	

Q6 For each of the following scenarios please indicate, using percentages, the frequency with which your decision to treat with low-dose Ara-C was shaped by patient preference. Please give a percentage If Vidaza (5-azacitidine) has significantly changed the way you make decisions, please consider how you made decisions before the product was available. (Summary of means)	
Scenario	Mean percentage
Suitable for low-dose Ara-C (Low-dose Ara-C given, accounting for patient preference)	44%
Borderline for low-dose Ara-C (Low-dose Ara-C given, accounting for patient preference)	36%
Unsuitable for low-dose Ara-C (Low-dose Ara-C given, accounting for patient preference)	26%

Q7 For each of the following scenarios please indicate, using percentages, the frequency with which your decision not to treat with low-dose Ara-C was shaped by patient preference. Please give a percentage If Vidaza (5-azacitidine) has significantly changed the way you make decisions, please consider how you made decisions before the product was available.		
	Total	
(Summary of coding)	N	%
Suitable for low-dose Ara-C (Low-dose Ara-C not given, accounting for patient preference)		
0%	11	15%
1-10%	15	21%
11-20%	14	19%
21-30%	10	14%
31-40%	5	7%
41-50%	7	10%
51-60%	0	0%
61-70%	2	3%
71-80%	3	4%
81-90%	0	0%
91-99%	0	0%
100%	5	7%
Mean	29%	
Base	72	
Borderline for low-dose Ara-C (Low-dose Ara-C not given, accounting for patient preference)		
0%	10	14%
1-10%	17	24%
11-20%	7	10%
21-30%	6	8%
31-40%	5	7%
41-50%	15	21%
51-60%	3	4%
61-70%	2	3%
71-80%	4	6%
81-90%	0	0%
91-99%	0	0%
100%	3	4%
Mean	32%	
Base	72	

[Q7 continued]

Unsuitable for low-dose Ara-C (Low-dose Ara-C not given, accounting for patient preference)		
0%	20	28%
1-10%	12	17%
11-20%	7	10%
21-30%	7	10%
31-40%	3	4%
41-50%	2	3%
51-60%	6	8%
61-70%	2	3%
71-80%	7	10%
81-90%	2	3%
91-99%	1	1%
100%	3	4%
Mean	32%	
Base	72	

Q7 For each of the following scenarios please indicate, using percentages, the frequency with which your decision not to treat with low-dose Ara-C was shaped by patient preference. Please give a percentage If Vidaza (5-azacitidine) has significantly changed the way you make decisions, please consider how you made decisions before the product was available. (Summary of means)	
Scenario	Mean percentage
Suitable for low-dose Ara-C (Low-dose Ara-C not given, accounting for patient preference)	29%
Borderline for low-dose Ara-C (Low-dose Ara-C not given, accounting for patient preference)	32%
Unsuitable for low-dose Ara-C (Low-dose Ara-C not given, accounting for patient preference)	32%

Appendix 3: Results tables from York registry

(on following page)