NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia

Final Scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of azacitidine within its licensed indication for the treatment of patients with higher risk (IPSS intermediate-II risk and high-risk) myelodysplastic syndrome, chronic myelomonocytic leukaemia, and acute myeloid leukaemia (<30% blasts).

Background

The myelodysplastic syndromes (MDS) are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS affects patients' quality of life due to debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions, and complications such as severe infections.

MDS are subdivided using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), the presence of chromosome 7 abnormalities, and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-I risk, intermediate-II risk or high-risk. It is estimated that higher risk MDS subgroups (intermediate-II and high-risk) form approximately 22% and 7% of the MDS population, respectively. The FAB system divides MDS into five subgroups, including chronic myelomonocytic leukaemia (CMML), which is characterised by high numbers of white blood cells in the blood and bone marrow. The WHO system, which divides MDS into eight subgroups, does not class CMML as a type of MDS, but rather within a new category of myelodysplastic-myeloproliferative overlap syndromes.

MDS are associated with an increased risk of transformation to acute myeloid leukaemia (AML). AML is a progressive form of MDS characterised by rapidly growing cancer of the blood and bone marrow. Around 30% of patients with MDS will progress to AML

There were 1,993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of diagnosis. Median survival of patients with MDS is around 20 months but can be less than 6 months for high

risk subgroups. Establishing the presence of chromosome 7 abnormalities is important as this is associated with rapid progression to AML.

The mainstay of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients. Stem cell transplant is not an option for the majority of patients since the patients' age and/or co morbidities usually precludes this treatment option.

The technology

Azacitidine (Vidaza, Celgene) is an anticancer drug that is thought to act by an epigenetic mechanism of action. Epigenetic therapies are thought to work by re-establishing cells' natural mechanisms to control abnormal growth rather than by causing cell death. Azacitidine is administered subcutaneously.

Azacitidine has received a positive opinion from the CHMP for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: IPSS intermediate-II and high-risk MDS; CMML with 10-29% marrow blasts without myeloproliferative disorder; or AML with 20-30% blasts.

Intervention	Azacitidine
Population	Adults who are not eligible for haematopoietic stem cell transplantation with higher-risk (IPSS intermediate-II risk and high-risk) myelodysplastic syndromes, chronic myelomonocytic leukaemia,or acute myeloid leukaemia (<30% blasts)
Comparators	• best supportive care (such as blood transfusions, erythropoietin and granulocyte-colony stimulating factor, with infection prophylaxis) • chemotherapy (such as cytarabine and anthracyclines)– low and high dose

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including time to transformation to AML or death) • response rates, including haematologic response and improvement • blood-transfusion independence • infections requiring IV therapy • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, consideration will be given to the subgroup of patients with chromosome 7 abnormalities. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: None Related Guidelines: Cancer Service Guidance, October 2003, Improving outcomes in haemato-oncology cancer.