NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of oral azacitidine within its marketing authorisation as maintenance treatment for adults with acute myeloid leukaemia after induction therapy.

Background

Acute myeloid leukaemia is a cancer of the blood and bone marrow. It is characterised by the overproduction of early immature myeloid cells (blasts). Acute myeloid leukaemia is classified into different types. In most types of acute myeloid leukaemia, the leukaemia cells are immature white blood cells. In other less common types, too many immature platelets or immature red blood cells form leukaemia cells. Anaemia, bleeding problems and serious infections are common symptoms of acute myeloid leukaemia.

The incidence of acute myeloid leukaemia has increased by 7% in the UK over the last decade.[1] There are around 3,200 new diagnoses of acute myeloid leukaemia in the UK per year.[1] The incidence rate increases with age with the highest rates being in the 85 to 89 age group.[1] There are around 2,600 acute myeloid leukaemia deaths registered in the UK per year.[1]

The aim of treatment for acute myeloid leukaemia is to cure it. For people who are fit enough to have intensive treatment, induction chemotherapy is initially given to achieve a remission. Up to 80% of younger adults and up to 60% of adults aged 60 years or older have complete remission with a standard induction therapy regimen of anthracycline and cytarabine.[2] For people with adverse risk factors, relapse rates are high and 5-year overall survival rates are low even after people have remission with chemotherapy.[3] After remission, further cycles of chemotherapy are sometimes given to reduce the risk of the leukaemia recurring (consolidation therapy). Maintenance therapy is long term treatment which may be given to prevent the cancer returning when it is in remission or to prolong remission. Although, maintenance therapy is not always given to people with AML. People with good general health may have a stem cell transplantation to replace damaged blood cells with healthy ones. However, the decision for transplantation includes response to chemotherapy, the individual's fitness, donor source, and the individual's choice. Therefore, some people may not be eligible or may choose not to have stem cell transplantation.

For people with untreated disease:

- NICE technology appraisal 552 recommends liposomal cytarabine-daunorubicin as a treatment option.

- NICE technology appraisal 545 recommends gemtuzumab ozogamicin with daunorubicin and cytarabine as a treatment option for people with de novo CD33-positive acute myeloid leukaemia.

- NICE technology appraisal 523 recommends midostaurin as a treatment option for newly diagnosed acute FLT3-mutation positive myeloid leukaemia with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy.

- NICE technology appraisal 399 does not recommend subcutaneous azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people 65 years or older who are not eligible for haematopoietic stem cell transplant.

- NICE technology appraisal 218 recommends subcutaneous azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplant and have acute myeloid leukaemia with 20-30% blasts and multilineage dysplasia according to the World Health Organization classification.

The only treatment option currently recommended by NICE as maintenance therapy for acute myeloid leukaemia is midostaurin, and it is only recommended for people who had complete response to midostaurin as induction and consolidation treatment in people with FLT-3 mutations.

The technology

Azacitidine (Onureg, Celgene, a BMS company) is an analogue of the nucleoside cytidine. It is incorporated into DNA of AML cells and may inhibit methyltransferases and reduce DNA methylation. Azacitidine is also incorporated into RNA of AML cells, which may reduce RNA methylation, decrease RNA stability and decrease protein synthesis. Oral azacitidine has a distinct pharmacokinetic profile from injectable azacitidine. This formulation of azacitidine is administered orally.

Oral azacitidine has a marketing authorisation in the UK for “maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT)”.

Intervention	Oral azacitidine as maintenance treatment
Population	Adults with acute myeloid leukaemia who have complete disease remission, or complete remission with incomplete blood count recovery, following induction therapy with or without consolidation treatment who are not eligible for, including those who choose not to proceed to, haematopoietic stem cell transplantation

Comparators	• Midostaurin • Established clinical management without oral azacitidine (which may include a watch and wait strategy with best supportive care, low dose cytarabine or subcutaneous azacitidine)
Outcomes	The outcome measures to be considered include: • overall survival • relapse free survival • 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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia' (2018) NICE technology appraisal 552. 'Gemtuzumab ozogamicin for untreated acute myeloid leukaemia' (2018) NICE technology appraisal guidance 545. 'Midostaurin for untreated acute myeloid leukaemia' (2018) NICE technology appraisal guidance 523. 'Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts' (2016) NICE technology

	appraisal guidance 399. 'Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia' (2011) NICE technology appraisal guidance 218. Review date April 2014. Appraisals in development (including suspended appraisals) 'Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia' (suspended) NICE technology appraisals guidance [ID1627]. Related Guidelines: 'Haematological cancers: improving outcomes' (2016). NICE Guideline 47. Related Quality Standards: 'Haematological cancers' (2017). NICE quality standard 150. Related NICE Pathways: Blood and bone marrow cancers (2021) NICE pathway.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019): Chapter 29 Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 3, 4 and 5.

References

1 Cancer Research UK (2016) Acute myeloid leukaemia (AML) statistics. Accessed June 2021.

2 Dohner et al. (2017) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129 (4): 424-447.

3 Medeiros, BC et al. (2019) Optimizing survival outcomes with post-remission therapy in acute myeloid leukemia. American Journal of Hematology 94: 803-811.