NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Midostaurin for untreated acute myeloid leukaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of midostaurin within its marketing authorisation for untreated, FLT3 mutation-positive acute myeloid leukaemia.

Background

Acute myeloid leukaemia is a cancer of the bone marrow characterised by the overproduction of early immature myeloid cells (blasts). According to the World Health Organization criteria, the blast count for diagnosing acute myeloid leukaemia should generally exceed 20%. 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.

FMS-like tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase, a type of cell-surface receptor, which plays a role in the proliferation, or increase, in the number of certain blood cells. The FLT3 mutation is associated with relatively poor prognosis because of disease relapse.[1]

The incidence of acute myeloid leukaemia in England is about 2,500 people per year.[2] About one-third of people with acute myeloid leukaemia have the FLT3 mutation.[1]

Acute myeloid leukaemia typically develops rapidly and is fatal if not treated. 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. The most commonly used induction chemotherapy drugs are cytarabine, daunorubicin, mitoxantrone, etoposide, idarubicin, and fludarabine. After remission, further cycles of chemotherapy are given to reduce the risk of the leukaemia recurring (consolidation therapy). The most commonly used drugs for consolidation chemotherapy are cytarabine, etoposide, amsacrine, and mitoxantrone. In some circumstances, people may be offered haematopoietic stem cell transplantation, if they are fit enough.

NICE technology appraisal guidance 218 recommends azacitidine for adults who are not eligible for haematopoietic stem cell transplantation and have

acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.

The technology

Midostaurin (Rydapt, Novartis) is a multi-targeted kinase inhibitor, which was found to inhibit FLT3 and other receptor tyrosine kinases. It is administered orally.

Midostaurin does not currently have a marketing authorisation in the UK for acute myeloid leukaemia. It has been studies in clinical trials in combination with induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy, followed by midostaurin maintenance, compared with induction and consolidation chemotherapy alone, followed by placebo maintenance, in adults with newly diagnosed, FLT3-mutated acute myeloid leukaemia with more than 20% blasts in the bone marrow based on the World Health Organization classification.

Intervention(s)	Midostaurin in combination with standard induction and consolidation chemotherapy followed by single agent maintenance therapy.
Population(s)	People with untreated, FLT3 mutation-positive acute myeloid leukaemia.
Comparators	Established clinical management without midostaurin
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-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 use of midostaurin is conditional on the presence of FLT3 mutation. The economic modelling should include the costs associated with diagnostic testing for FLT3 mutation in people with acute myeloid leukaemia who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	If the evidence allows, a scenario analysis will be considered whereby stem cell transplant is included as a subsequent treatment for people who are fit enough to undergo the procedure and whose disease remitted after standard high-dose chemotherapy with or without midostaurin. This should reflect the proportion of people who proceed to stem cell transplant after each treatment regimen, as well as the costs and quality-adjusted life year benefits of the procedure. 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: 'Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts' (2016). NICE Technology Appraisal 399. Review date July 2019. 'Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia' (2011). NICE Technology Appraisal 218. Guidance on static guidance list. Terminated appraisals 'Decitabine for the treatment of acute myeloid leukaemia' (terminated appraisal) (2012). NICE

	Technology Appraisal 270. Appraisals in development (including suspended appraisals) 'Vosaroxin for treating relapsed or refractory acute myeloid leukaemia' NICE technology appraisals guidance [ID746]. Publication expected July 2017. Related guidelines 'Haematological cancers: improving outcomes' (2016). NICE Guideline 47. Review date to be confirmed. Related NICE Pathways: Blood and bone marrow cancers (2016) NICE pathway
Related National Policy	NHS England (2016) Manual for Prescribed Specialised Services 2016/17. Chapters 29, 105. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf **National Service Frameworks** Cancer **Department of Health** Department of Health (2014) NHS outcomes framework 2015-2016 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1 Small D (2006) FLT3 mutations: biology and treatment. Hematology Am Soc Hematol Educ Program 2006: 178-84.

2 Cancer Research UK (2013) Acute myeloid leukaemia (AML) incidence statistics. Accessed August 2016.