NHS England

Clinical Commissioning Policy Proposition:

Clofarabine for refractory or relapsed acute myeloid leukaemia (AML) as a bridge to stem cell transplantation

Reference: NHS England 1602

First published: TBC

Prepared by NHS England Specialised Services Clinical Reference Group for Chemotherapy

Published by NHS England, in electronic format only.

Contents

1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About acute myeloid leukaemia

Acute myeloid leukaemia (AML) is a type of blood cancer that affects the white blood cells, specifically myeloid cells. The disease is relatively rare and is often diagnosed in people above 65 years of age. It is considered to be an aggressive and rapidly progressing cancer that almost always requires immediate treatment.

AML causes white blood cells to be produced more quickly than normal and as a result the cells become abnormal because they grow and divide too fast. The abnormal myeloid cells build-up in the blood and bone marrow and eventually can spread to other parts of the body. People with AML will usually experience more infections, tiredness, high temperature, breathlessness and they may bruise or bleed more easily.

About current treatments

Treatment for AML usually is divided into two phases, induction and consolidation. The aim of the induction phase is to destroy the cancer cells, this is called inducing a remission. Following the induction phase, more treatment is given to stop, or consolidate, the cancer from retunring. In both phases, chemotherapy is the main treatment option, however, some patients may also have a stem cell transplant as part of consolidation treatment.

In some cases, AML can return, or relapse, following a period of remission after first treatment and some patients are resistant to the chemotherapy medicines that are used, this is called refractory disease. This policy proposition relates to relapsed and refractory disease, this means that each patient will have had at least one prior, or first line, treatment.

About the new treatment

Clofarabine is a chemotherapy medicine which belongs to a group of drugs known as anti-metabolites. These drugs interfere with the growth of cancer cells and cause them to die. Clofarabine is delivered intravenously (injected into the bloodstream) and can be used to treat AML when combined with another drug called cytarabine, which is usually used to treat AML alone. In both cases, the aim of treatment is usually to induce remission and enable a stem cell transplant.

What we have decided

NHS England has carefully reviewed the evidence to treat refractory or relapsed AML with clofarabine alone or in combination with cytarabine**.** We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission clofarabine for this indication.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether clofarabine will be routinely commissioned for refractory or relapsed AML with intent to bridge to stem cell transplantation is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Clinical Indication

Acute Myeloid Leukaemia (AML) is a type of cancer affecting the blood, characterised by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production or normal blood cells leading to anaemia, bleeding problems and serious infections.

Symptoms may be related to bone marrow failure (causing anaemia, neutropenia and thrombocytopenia) or organ infiltration (usually liver or spleen). Fever is a common presenting sign, and symptoms include fatigue, dizziness, shortness of breath on exertion, bleeding and bone pain. AML develops rapidly and is fatal if not treated.

The aim of treatment for AML is usually to achieve a remission of the disease through suppression of the patient's own haemopoetic cells (in the bone marrow). Once disease remission is achieved, a haemopoetic stem cell transplant (HSCT) can be given, replacing the haemopoetic system, but without the abnormal white blood cell line. A number of chemotherapy medicines are currently available to treat AML and provide a bridge to HSCT; for patients with refractory or relapsed AML, European LeukemiaNet guidelines recommend cytarabine (if not used for first induction), with or without an anthracycline (Döhner et al, 2010). Mitoxantrone plus

etoposide and cytarabine (MEC) is another option for relapsed disease.

Proposed Intervention

Clofarabine is a purine nucleoside antimetabolite – a form of systemic chemotherapy, which can be used in combination with cytarabine (another systemic chemotherapeutic agent) for the treatment of refractory or relapsed AML. It is not included in European AML guidelines and is not licensed for this indication.

Where clofarabine is given to treat relapsed and refractory AML, it is administered intravenously at a dose of 40mg/m2 daily on days one to five of a twenty-one day cycle.

4 Definitions

Acute Myloid Leukaemia (AML) – a form of aggressive (acute) leukaemia which affects the myloid cells and causes the build-up of abnormal white blood cells.

Clofarabine – an anti-metabolite drug treatment which aims to treat leukaemia through interfereing with the growth of abnormal cancerous cells.

Complete Remission (CR) – no detectable disease following a course of treatment.

Consolidation – the second phase of treatment for cancers such as AML, which takes place after remission has been induced. This part of treatment aims to prevent a relapse from occurring.

Hematopoietic stem cell transplantation (HSCT) – this is a form of stem cell transplantation that is used to treat certain patients with a range of malignant and non-malignant blood-related disorders. It involves the use of stem cells (from the patient or a donor).

Induction – the first phase of treatment for cancers such as AML, which aims to induce remission. This part of treatment aims to destroy as many leukemia cells as possible.

Overall Survival (OS) – the length of time from either diagnosis or start of treatment that the patient is still alive.

Progression Free Survival (PFS) – the length of time from either diagnosis or start of treatment to disease progression or patient death from any cause.

Relapsed disease – describes when a condition has recurred following response to previous treatment, this may occur at any time following completion of treatment.

Refractory disease – means that there has been no response to the immediately preceding treatment, patients have either progressed during treatment or have stable disease whenever treatment has been stopped.

5 Aims and Objectives

This policy proposition considered clofrarbine as a treatment for refractory or relapsed AML with intent to bridge to transplant.

The objectives were to establish, via an evidence review, the following:

- Does clofarabine improve response rate in patients with refractory or relapsed AML allowing them to undergo stem cell transplantation and thereby prolong survival?

6 Epidemiology and Needs Assessment

The incidence of AML in Europe is 5-8 cases per 100,000 people. In 2013, there were 2,942 new cases of AML in the UK. Based on current population estimates, the number of new cases in England in a given year will amount to approximately 2,489 (Cancer Research UK).

Incidence increases with age and median age of onset is 67 years. Between 2011 and 2013, about 55% of cases were diagnosed in people aged 70 years and over. Complete remission is achieved in 60- 80% of patients (Patient.info).

Patients who do not achieve complete remission, or who subsequently relapse,

usually undergo further chemotherapy, still with a view to achieving remission. Relapse occurs in over 50% of patients at some point.

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Evidence Summary

There is one randomised, controlled clinical trial of clofarabine in patients with refractory or relapsed AML (Faderl et al 2012). The CLASSIC I trial randomised 326 adults with relapsed or refractory AML to clofarabine 40mg/m^2 or placebo daily for five days, given as an intravenous infusion over one hour, followed three hours later by a two-hour infusion of cytarabine 1g/m^2.

Evidence for efficacy of clofarabine

Significantly more patients receiving clofarabine plus cytarabine achieved complete remission compared to patients receiving cytarabine monotherapy (35.2% vs. 17.8%; $p<0.01$). However, similar numbers of patients in each group subsequently underwent HSCT (about 20%). There was no significant difference between groups in the primary outcome of median overall survival (6.6 months with clofarabine plus cytarabine vs. 6.3 months with placebo plus cytarabine). Median disease-free survival was also similar between groups (8.1 months vs. 7.0 months, respectively). No comparison of post-transplant outcomes was reported for patients who did vs. those who did not go onto receive HSCT. The study enrolled patients aged at least 55 years, who had received no more than two previous induction regimens. It involved few European patients so the results may not be generalisable to the UK. In addition, the CLASSIC I trial was not designed to assess whether use of clofarabine allows more patients to undergo HSCT.

The authors of one retrospective study (Roberts et al, 2015) noted that only ten of the 65 patients who received clofarabine and cytarabine in their study would have been eligible for CLASSIC I, mostly because of younger age. In CLASSIC I, there were slightly more patients in the clofarabine group than in the placebo group with

unfavourable/other cytogenetics (49.4% vs. 38.6%, respectively) and worse performance status (ECOG 2, 16.0% vs. 11.4%, respectively), indicating they were possibly less likely to respond to or tolerate treatment, but otherwise baseline characteristics were similar between groups.

CLASSIC I did not report overall survival rates for the subgroup of patients who proceeded to HSCT; for all enrolled patients, overall survival at two years was estimated by other investigators to be about 10% (Middeke et al, 2016), a rate much lower than reported in uncontrolled studies. A retrospective study involving 59 patients showed that clofarabine was not associated with improved survival compared to two mitoxantrone-containing regimens (Loeffler et al, 2015).

Evidence for safety of clofarabine

There was a high mortality rate of 16% in the first 30 days after administration of clofarabine and cytarabine, compared with 5% in patients treated with cytarabine alone ($p<0.01$). Deaths were mostly due to adverse events, and this might explain why an increase in complete remission rate did not translate into improved overall survival. Serious adverse events occurred in 60% of patients given clofarabine and cytarabine, and 49% given cytarabine alone. Serious infections occurred in 38% of patients given clofarabine and cytarabine compared with 22% of patients given cytarabine alone. Most common grade 3 to 4 adverse events in the clofarabine group were febrile neutropenia, hypokalaemia, thrombocytopenia, pneumonia, anaemia, neutropenia, and increased liver enzymes.

Uncontrolled studies using doses of clofarabine ranging from 15mg/m^2 to 40mg/m^2, alone or with cytarabine, show it can be used as a bridge for reducing leukaemic burden prior to HSCT in some patients. However, these findings are at high risk of bias and are limited by patient, disease and treatment heterogeneity.

Conclusion

There is only one randomised controlled trial of clofarabine in refractory or relapsed AML in older adults aged at least 55 years, and this showed that adding clofarabine 40mg/m2 daily for five days to treatment with cytarabine does not allow more patients to undergo HSCT or improve overall survival. However, the study was not

designed to assess whether use of clofarabine allows more patients to undergo HSCT. More patients achieved complete remission with clofarabine and cytarabine than with cytarabine alone, but this was offset by more deaths due to adverse events. No comparison of post-transplant outcomes was reported for patients who did vs. those who did not go onto to receive HSCT.

The optimal role for clofarabine is unclear, and there are still questions to be answered about the balance between efficacy and toxicity of clofarabine. Insufficient evidence is available to determine the most appropriate dose and which patient groups are most likely to tolerate clofarabine.

8 Proposed Criteria for Commissioning

Not applicable

9 Proposed Patient Pathway

Not applicable

10 Proposed Governance Arrangements

Not applicable

11 Proposed Mechanism for Funding

Not applicable

12 Proposed Audit Requirements

Not applicable

13 Documents That Have Informed This Policy Proposition

This document updates and replaces:

- NHS England. National Cancer Drugs Fund List. Ver 6.0. Date published: 4/11/15. http://webarchive.nationalarchives.gov.uk/20151223153822/https://www.england.nhs.uk/wp-content/uploads/2015/11/ncdf-list-nov-15.pdf

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

Cancer Research UK. Acute myeloid leukaemia (AML) statistics. Accessed 2/09/16. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml

Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukaemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010; 115: 453-474.

Faderl S, Wetzler M, Rizzieri D, et al. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukaemia: Results from the CLASSIC I trial. J Clin Oncol 2012; 30: 2492-2499.

Loeffler C, Kapp M, Grigoleit G-U, et al. Control of relapsed or refractory acute myeloid leukemia by clofarabine in preparation for allogeneic stem cell transplant. Leukemia Lymphoma 2015; 56: 3365-3369.

Middeke JM, Herbst R, Parmentier S, et al. Clofarabine salvage therapy before allogeneic hematopoietic stem cell transplantation in patients with relapsed or refractory AML: results of the BRIDGE trial. Leukemia 2016; 30: 261-267.

National Comprehensive Cancer Network. National Clinical Practice Guidelines in Oncology (NCCN Guidelines). Acute myeloid leukemia. Version 2.2016. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Patient.info. Acute myeloid leukaemia. Last checked 11/03/16. http://patient.info/doctor/acute-myeloid-leukaemia-pro

Roberts DA, Wadleigh M, McDonnell AM, et al. Low efficacy and high mortality associated with clofarabine treatment of relapsed/refractory acute myeloid leukemia and myelodysplastic syndromes. Leukemia Research 2015; 39: 204-210.