NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of liposomal cytarabine and daunorubicin within its marketing authorisation for untreated, high risk, acute myeloid leukaemia.

Background

Acute myeloid leukaemia (AML) is a bone marrow cancer characterised by the overproduction of early immature myeloid cells (blasts). Myeloid neoplasms with more than 20% blasts in the peripheral blood or bone marrow are considered AML. AML is classified into several different types. In most types of AML, the leukaemia cells are immature white blood cells. In other less common types, too many immature platelets or immature red blood cells form the leukaemia cells. Anaemia, bleeding problems and serious infections are common symptoms in AML.

The incidence of AML in the UK is about 3100 cases per year. Around three quarters of all cases occur in people over 60 years and 55% of all cases occur in people over 70 years[1]. AML is slightly more common in men than in women.

AML is classified according to the World Health Organisation (WHO) classification which takes into account morphology, cytochemistry, immunophenotype, cytogenetics and clinical information and categorises AML into several clinically distinct types. Cytogenetics is the most important prognostic factor and classifies patients into 'favourable, intermediate or adverse risk' groups based on the presence or absence of specific chromosomal patterns. Poor prognostic factors, including intermediate and adverse risk cytogenetics, are more common in older people and make treatment more challenging.

AML typically develops rapidly and can be fatal unless treated. People for whom intensive chemotherapy is suitable are treated with cytotoxic agents such as an anthracycline in combination with cytarabine to induce remission. People who cannot tolerate or do not wish to receive intensive chemotherapy may have dose reductions or are given non-intensive chemotherapy such as low dose cytarabine[2]. NICE technology appraisal guidance No. 218 recommends azacitidine for adults with acute myeloid leukaemia with 20–30%

blasts and multilineage dysplasia (AML that has developed from a myelodysplastic syndrome), according to the WHO classification and who cannot have haematopoietic stem cell transplantation. Azacitabine is not recommended by NICE for people with more that 30% blasts (NICE technology appraisal 399). If a person's leukaemia is in remission they may receive consolidation therapy or a haematopoietic stem cell transplant if suitable[2]. Other aspects of care include blood product replacement for anaemia and thrombocytopenia, antibiotics and antifungals for infections and intermittent low dose chemotherapy with hydroxycarbamide to keep the peripheral blood blast count low.

The technology

Liposomal cytarabine and daunorubicin (CPX-351, brand name unknown, Jazz Pharmaceuticals) is a liposomal encapsulated combination of cytarabine and daunorubicin. It is delivered by intravenous infusion. The dosing schedule differs from standard intensive induction therapy with cytarabine and daunorubicin.

Liposomal cytarabine and daunorubicin does not have a marketing authorisation for the treatment of acute myeloid leukaemia. It has been studied in a clinical trial in people aged 60 to 75 diagnosed with high risk AML, with at least 20% blasts in the peripheral blood or bone marrow. Liposomal cytarabine and daunorubicin was compared with a '3 + 7 regimen' of cytarabine administered by continuous infusion for 7 days and daunorubicin given on days 1,2 and 3. In the trial liposomal cytarabine and daunorubicin was administered by a 90 minute infusion on days 1, 3 and 5.

Intervention(s)	Liposomal cytarabine and daunorubicin
Population(s)	People with newly diagnosed, high risk, AML who are considered to be eligible for intensive therapy
Comparators	• Standard intensive induction therapy • Azacitidine (for people who are not eligible for haematopoietic stem cell transplantation and have AML with 20-30% blasts and multilineage dysplasia)

Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-free-survival • remission • 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 patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.
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. On static list. Terminated appraisals 'Decitabine for the treatment of acute myeloid leukaemia' (terminated appraisal) (2012). NICE Technology Appraisal 270. Appraisals in development (including suspended appraisals) 'Midostaurin for untreated acute myeloid leukaemia'

	NICE technology appraisals guidance [ID894]. Publication expected April 2018. 'Decitabine for acute myeloid leukaemia' NICE technology appraisals guidance [ID1114]. Publication expected February 2018 'Gemtuzumab ozogamicin for treating acute myeloid leukaemia' NICE technology appraisal guidance [ID982]. Publication expected July 2018 Related Guidelines: 'Haematological cancers: improving outcomes' (2016). NICE guideline 47 Review date to be confirmed. Related Quality Standards: http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp 'Haematological cancers' (2017) Quality standard 150. Related NICE Pathways: Blood and bone marrow cancers (2017) NICE pathway http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	NHS England (2013) 2013/14 NHS standard contract for cancer: chemotherapy (adult) – service specification NHS England (2016) Manual for Prescribed Specialist Services 2016/17. Chapters 29,105 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 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

Questions for consultation

What clinical criteria are taken into account when deciding whether intensive chemotherapy is a suitable treatment for a person with acute myeloid leukaemia?

How is high risk acute myeloid leukaemia defined?

Have all relevant comparators for liposomal cytarabine and daunorubicin been included in the scope? Which treatments are considered to be established clinical practice in the NHS for newly diagnosed acute myeloid leukaemia?

Would liposomal cytarabine and daunorubicin be used as an alternative to azacitidine in the population for whom azacitidine is recommended in NICE technology appraisal guidance 218?

What consolidation therapy would be used following remission on liposomal cytarabine and daunorubicin? Would liposomal cytarabine and daunorubicin be used as a consolidation therapy following remission?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom liposomal cytarabine and daunorubicin is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider liposomal cytarabine and daunorubicin will fit into the existing NICE pathway, blood and bone marrow cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which liposomal cytarabine and daunorubicin will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider liposomal cytarabine and daunorubicin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of liposomal cytarabine and daunorubicin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic.

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Cancer Research UK. Acute Myeloid Leukaemia incidence statistics accessed July 2017

2 Döhner H, Estey EH, Amadori et al. (2010) Diagnosis and management of acute myeloid leukemia in adults: recommendations form an international expert panel, on behalf of the European LeukemiaNet