NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of treosulfan with fludarabine within its marketing authorisation as a conditioning treatment for malignant diseases prior to allogeneic haematopoietic stem cell transplantation.

Background

An allogenic haematopoietic stem cell transplantation (HSCT) involves replacing the bone marrow stem cells of a patient (after high-dose therapy), with stem cells from a tissue-type matched or mismatched donor. It is a potentially curative treatment for various haematological malignancies such as myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML). Clinical guidelines recommend identifying patients with MDS who are suitable for HSCT at diagnosis because this therapy has the greatest curative potential.[2] Similarly, HSCT is a potentially curative treatment for AML and should be offered to patients with high risk of relapse.[3]

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. Anaemia, bleeding problems and serious infections are common symptoms in AML. Cytogenetics is the most important prognostic factor and classifies patients into 'favourable, intermediate or unfavourable risk' groups based on the presence or absence of specific chromosomal patterns.

The MDS are a group of conditions where the bone marrow produces blood cells that are not fully developed. 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 are associated with an increased risk of transformation to AML. Around 30% of patients with MDS will progress to AML. The International Prognostic Scoring System (IPSS) classifies outcome as low-risk, intermediate-1 risk, intermediate-2 risk or high-risk. Around 70% of all MDS is either low risk or intermediate-1 risk.

There were 2,163 people newly diagnosed with MDS in England in 2016, with over 90% of patients aged over 60 years at the time of diagnosis.[1] There were 2,376 people newly diagnosed with AML in England in 2016 with over 75% of patients aged over 60 years at the time of diagnosis.[1]

Once AML or MDS has been successfully treated, there may be a significant risk of the condition developing again. Before a patient receives HSCT they need to have a type of treatment called a 'conditioning therapy' which prepares the body by eradicating the disease and suppressing the immune reactions. Standard high-dose intensity conditioning regimens are associated with morbidity and mortality and are generally used in people who are younger and more able to tolerate treatment.[5] Standard high-dose intensity conditioning for AML include: cyclophosphamide and total body irradiation, cyclophosphamide and busulfan, or fludarabine and busulfan. Reduced intensity conditioning is also used if treatment is less likely to be tolerated or if there are comorbidities.[3]

The technology

Treosulfan (Trecondi, Medac GmbH) is the prodrug of a bifunctional sulfonate alkylating agent with myeloablative, immunosuppressive, and antineoplastic activities. It is administered intravenously.

Treosulfan in combination with fludarabine is a myeloablative reduced-toxicity conditioning treatment. This treatment has been shown to be myeloablative (as indicated by profound, long-lasting and usually irreversible marrow aplasia).

Treosulfan with fludarabine does not have a marketing authorisation as a conditioning treatment before HSCT for malignant diseases. It has been studied in a clinical trial compared with busulfan with fludarabine as a conditioning treatment before allogeneic haematopoietic stem cell transplant in adults with haematological malignant disease (AML or MDS) that is in remission. It has also been studied in children and young people with haematological malignant disease.

Intervention(s)	Treosulfan with fludarabine
Population(s)	Adults, children and young people with malignant disease that is in remission before allogenic haematopoietic stem cell transplantation
Comparators	Conditioning treatments (either high dose or reduced intensity): • cyclophosphamide and total body irradiation • cyclophosphamide and busulfan • busulfan with fludarabine • established clinical management without treosulfan with fludarabine

Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • rates of relapse • success of stem cell transplantation (engraftment) • 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	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. 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. (2018) NICE technology appraisals guidance 523. Review date June 2021.

	Decitabine for acute myeloid leukaemia. NICE technology appraisals guidance [ID1114]. Suspended. Gemtuzumab ozogamicin for treating acute myeloid leukaemia. NICE technology appraisal guidance [ID982]. Publication expected Nov 2018. **Related guidelines**: Haematological cancers: improving outcomes (2016). NICE guideline 47. Review date to be confirmed. **Related quality standards**: Haematological cancers (2017) Quality standard 150. **Related NICE Pathways**: Blood and bone marrow cancers (2017) NICE Pathway
Related National Policy	Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS England, National Cancer Drugs Fund List, September 2016. Department of Health, Improving Outcomes: A strategy for cancer, fourth annual report, Dec 2014. Department of Health, Cancer commissioning guidance, December 2009. NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)

Questions for consultation

When is haematopoietic stem cell transplant used in clinical practice for haematological malignant diseases (for example is this only in patients with high risk of relapse and does this differ by the type of malignant disease)?

Have all relevant comparators for treosulfan with fludarabine been included in the scope?

- Where in the treatment pathway is conditioning treatment for haematological malignant disease used?
- In clinical practice what conditioning therapies are used before haematopoietic stem cell transplant for haematological malignant disease?
- Are different conditioning therapies used for different types of malignant disease, if so, please specify?

- Should high dose intensity conditioning treatments be included as comparators, if so, please specify?
- Are the same conditioning therapies used in children and young people, if not, please specify?

Are the outcomes listed appropriate?

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

Where do you consider treosulfan with fludarabine 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 treosulfan with fludarabine 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 treosulfan with fludarabine 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 treosulfan with fludarabine 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.

- Would it be appropriate to use the cost comparison methodology for 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 technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Office for National Statistics. Cancer registration statistics, England: 2016. Accessed October 2018

2 Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M et al. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. British Journal of Haematology. 2013 Dec; 164(4): 503-525.

3 Kassim AA, Savani BN. Hematopoietic stem cell transplantation for acute myeloid leukemia: A review. Hematology/Oncology and Stem Cell Therapy. 2017 Dec; 10(4): 245-251.

4 Casper J, Holowiecki J, Trenschel R, Wandt H, Schaefer-Eckart K, Ruutu T et al. Allogeneic hematopoietic SCT in patients with AML following treosulfan/fludarabine conditioning. Bone Marrow Transplantation. 2012; 47:1171-1177.