NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant

Final 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 conditioning 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). About 50% of all allogenic HSCTs are currently done to treat AML or MDS. Clinical guidelines recommend identifying patients with MDS who are suitable for allogenic HSCT at diagnosis because this therapy has the greatest curative potential.[2] Similarly, allogenic HSCT is a potentially curative treatment for AML and should be offered to patients with high risk of relapse.[3]

Registry data from the British Society of Blood and Marrow Transplantation (BSBMT) shows that over 3780 allogenic stem cell transplants were carried out in the UK in 2017 for non-malignant diseases prior to HSCT.

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 myeloablative 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 high-dose busulfan. Thiotepa is also licensed as a conditioning treatment before allogenic stem cell transplant with or without total body irradiation. Reduced intensity conditioning is also used if treatment is less likely to be tolerated or if there are comorbidities.[3] Reduced intensity conditioning regimens include low-dose busulfan and fludarabine or melphalan and fludarabine.

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).

The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending treosulfan in combination with as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases.

Intervention(s)	Treosulfan with fludarabine
Population(s)	People with malignant disease that is in remission before allogenic haematopoietic stem cell transplantation
Comparators	Standard high-dose intensity (myeloablative) conditioning regimens: • cyclophosphamide and total body irradiation • cyclophosphamide and busulfan • cyclophosphamide and thiotepa • high-dose busulfan with fludarabine with or without thiotepa Reduced intensity conditioning regimens: • low-dose busulfan with fludarabine • melphalan plus fludarabine
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • 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**: none **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)

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.