NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Melphalan for haematological diseases before allogeneic haematopoietic stem cell transplant

Draft scope

Draft remit/appraisal objective

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

Background

An allogeneic haematopoietic stem cell transplantation (allo-HSCT) involves replacing the bone marrow stem cells of a person (after conditioning therapy), with stem cells from a tissue-type matched or mismatched donor. Bone marrow, peripheral blood stem cells, or umbilical cord blood stem cells may be used as donor stem sources. Allo-HSCT is a potentially curative treatment for various malignant and non-malignant haematological disorders, including myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML), and other disorders of the immune system.[1,2] About 50% of all allo-HSCTs are currently done to treat AML or MDS.[3] Clinical guidelines recommend identifying patients with MDS who are suitable for allo-HSCT at diagnosis because this therapy has the greatest curative potential.[2] Similarly, allo-HSCT is a potentially curative treatment for AML and should be offered to patients with high risk of relapse.[4]

Registry data from the British Society of Blood and Marrow Transplantation shows that 1,476 allogeneic stem cell transplants were carried out in the UK and Republic of Ireland in 2020.[3] Of these, 1,165 (79%) were first transplants for haematological diseases.[3]

Before someone can have allo-HSCT, they need to have a type of treatment called 'conditioning therapy'. Conditioning therapy prepares the body by eradicating the disease and suppressing the immune reactions. Standard high-intensity myeloablative conditioning (MAC) regimens are associated with morbidity and non-relapse mortality, and are generally used in people who are younger and more able to tolerate treatment.[5] Standard high-intensity MAC regimens for haematological diseases include: cyclophosphamide and total body irradiation, cyclophosphamide and busulfan, or fludarabine and high-dose busulfan. Thiotepa is also licensed as a conditioning treatment before allo-HSCT with or without total body irradiation. Reduced intensity conditioning is also used if treatment is less likely to be tolerated, or if someone has comorbidities. NICE technology appraisal 640 recommends treosulfan with fludarabine for people with malignant diseases for whom a reduced intensity regimen would be suitable. Reduced intensity conditioning regimens also include low-dose busulfan and fludarabine or melphalan and fludarabine.

The technology

Melphalan (PHELINUN, Adienne Pharma & Biotech), in combination with other cytotoxic medicinal products, has a marketing authorisation in the UK as:

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- a reduced intensity conditioning treatment prior to allo-HSCT in malignant haematological diseases in adults, and
- a conditioning regimen prior to allo-HSCT in the paediatric population as:
    - myeloablative conditioning treatment in case of malignant haematological diseases
    - reduced intensity conditioning treatment in case of non-malignant haematological diseases.

Intervention	Melphalan in combination with other cytotoxic medicinal products
Population	People with haematological disease prior to allogeneic haematopoietic stem cell transplantation
Subgroups	If the evidence allows the following subgroups will be considered: • people with malignant haematological disease • people with non-malignant haematological disease • people for whom standard high-intensity conditioning treatment is suitable.
Comparators	Standard high-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: • treosulfan with fludarabine • 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.

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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 commercial arrangements for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.
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	**Related Technology Appraisals:** **'**Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant' (2020). NICE Technology appraisal guidance 640. Review date 2023. **Related Guidelines:** 'Myeloma: diagnosis and management' (2018). NICE guideline 35. Review date to be confirmed. 'Haematological cancers: improving outcomes' (2016). NICE guideline 47. Review date to be confirmed. 'COVID-19 rapid guideline: haematopoietic stem cell transplantation' (2021). NICE guideline 164. Review date to be confirmed. **Related Quality Standards:** 'Haematological cancers' (2017) NICE quality standard 150.
Related National Policy	Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages), 2015. Clinical Commissioning Policy Clinical Commissioning Policy: Allogeneic Haematopoietic Stem Cell Transplant for Primary Immunodeficiencies (all ages), 2019. Clinical Commissioning Policy Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML, 2016. Clinical guidelines

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	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)

Questions for consultation

When is allo-HSCT used in clinical practice for malignant haematological 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 melphalan been included in the scope?

- Where in the treatment pathway is conditioning treatment (followed by allo-HSCT) used for malignant haematological disease?
- In clinical practice what conditioning therapies are used before allo-HSCT for malignant haematological diseases?
- Are different conditioning therapies used for different types of malignant disease? If so, please specify.
- In clinical practice what conditioning therapies are used before allo-HSCT for non-malignant haematological diseases?

Which treatments would melphalan be used in combination with?

Are the outcomes listed appropriate?

Would melphalan be a candidate for managed access?

Are the suggested subgroups appropriate? Are there any subgroups of people in whom melphalan is expected to be more clinically effective and cost effective or other groups that should be examined separately?

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 melphalan is 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 melphalan 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)?

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Do you consider that the use of melphalan 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 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 evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

References

1. Khorochkov A, Prieto J, Singh KB, et al. (2021) The Role of Allogeneic Stem Cell Transplantation in Multiple Myeloma: A Systematic Review of the Literature. Cureus 13(9).
2. Killick SB, Carter C, Culligan D et al. (2013) Guidelines for the diagnosis and management of adult myelodysplastic syndromes. British Journal of Haematology 164(4): 503-525.
3. British Society of Blood and Marrow Transplantation and cellular therapy (2020). UK & ROI Transplant Activity Table by Disease. Accessed February 2022.
4. Kassim AA, Savani BN. (2017) Hematopoietic stem cell transplantation for acute myeloid leukemia: A review. Hematology/Oncology and Stem Cell Therapy 10(4): 245-251.
5. Kamal A, Zar MA, Fazeel HM et al. (2018). Reduced-Intensity Conditioning Versus Myeloablative Conditioning for Allogeneic Hematopoietic Cell Transplantation in Patients with Myelodysplastic Syndrome: A Systematic Review and Meta-Analysis of Randomized Trials. Blood 132 Supplement 1: 5770.

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