NHS England

Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages)

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Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages)

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Policy Statement

NHS England will routinely commission the use of second allogeneic haematopoietic stem cell transplant for relapsed disease for patients meeting the criteria set out in section 7. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

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 the new treatment

In illnesses such as cancer, relapsed disease is when the signs and symptoms return after a period of remission (being free of disease).

Haematopoietic stem cell transplantation (HSCT) is also known as blood and marrow transplantation (BMT).

- Allogeneic HSCT is a particular type of blood and bone marrow transplant.
- It involves replacing damaged blood cells with healthy ones from someone else (a donor).

It is used to treat carefully selected patients with a range of blood problems (cancerous and non-cancerous) and other illnesses that affect the immune system.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed disease with second allogeneic haematopoietic stem cell transplant. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a policy to routinely commission second allogeneic HSCT transplant for a small number of highly selected patients with relapsed disease.

Allogeneic haematopoietic stem cell transplant (Allo-HSCT) is used in the management of haematological malignancy to generate an anti-tumour immune response by replacing host bone marrow and immune system, usually after high dose of chemotherapy or radiotherapy. Allo-HSCT relies on a donor, and the donor and recipient are usually suitably matched for major histocompatibility complex antigens (MHC), routinely tested on white blood cells. Closer matches are generally possible when a sibling donor is available. Alternatively, a suitably matched unrelated donor may be used, and alternative donor sources, such as mismatch unrelated and halpo-identical family donors, may be used in the absence of a fully matched donor. Stem cells are derived from bone marrow, peripheral blood and umbilical cord.

Although Allo-HSCT may be potentially curative in a range of haematological malignancies, disease relapse after a first transplant remains a significant problem and is the major cause of post-transplant mortality in some conditions, such as myelodysplasia. The prognosis for patients with any haematological malignancy relapsing after an initial Allo-HSCT is poor, though the timeframe in which they relapse alters their prognosis (<3 months vs 3-12 months vs >12 months following Allo-HSCT). The best therapeutic option for patients that relapse after their first Allo-HSCT is uncertain. Options include: further chemotherapy; withdrawal of immunosuppressive treatment (given to reduce graft-versus-host disease) in order to enable a graft-versus-leukaemia response; infusion of donor lymphocytes; treatment with cytokines; or a second Allo-HSCT.

2 Definitions

Allogeneic haemopoietic stem cell transplantation (Allo-HSCT) is used to treat carefully selected patients with a range of malignant and non-malignant haematological disorders and other specific disorders of the immune system. It involves replacing the bone marrow stem cells of a patient following high-dose therapy, with stem cells from a tissue-type matched or mismatched donor.

Relapsed disease is a recurrence of the disease.

Haematological malignancies are tumours that affect the blood, bone marrow, lymph, and lymphatic system.

MHC antigens are a group of genes that help the immune system recognise foreign substances. They stimulate an organism's immunological response to transplanted organs and tissues and are originally defined as the most important molecule involved in the rejection of these.

Graft-versus-host disease is a common complication following an Allogeneic transplant where white blood cells (immune cells) in the donor cells (the graft) recognise the recipient host as "foreign". The transplanted white blood cells then attack the host's body cells.

Graft-versus-leukaemia response is the desired effect following Allo-HSCT where donor cells eliminate malignant cells.

3 Aims and Objectives

The policy document aims to define the commissioning position: second allogeneic haematopoietic stem cell transplants will be commissioned routinely by NHS England.

4 Epidemiology and Needs Assessment

HSCT offers a potential long-term curative option for a range of haematological malignancies but is associated with high treatment related mortality. Repeat transplant may be considered for primary graft failure/failure of engraftment and this is routinely commissioned.

Repeat transplant for treatment of relapse of the underlying disease is the focus of this policy. Relapse is the major cause of mortality in patients who have had an initially successful transplant. Post-transplant relapse rates vary by underlying condition and by clinical state at first transplantation (for example, whether the transplant was done in first or second remission; whether or not complete remission had been achieved at the time of transplantation, etc.).

The five-year incidence of relapse in low and intermediate risk leukaemias undergoing first Allo-HSCT in one US centre was reported as 32% (Carlens et al., 1998). For acute lymphoblastic leukaemia, a five-year relapse rate of 29% (+/- 9%) has been reported for patients transplanted whilst in first remission; and a rate of 52% (+/-8%) for patients transplanted in second remission (Barrett et al., 1989).

Data from NHS England suggests, over a 10 calendar year period (2000-2009, inclusive), 184 patients underwent a second Allo-HSCT for relapsed disease, primarily for acute myeloid leukaemia (AML 51%, CML 14%, lymphoma 7%, myeloma 2% & MDS 25%). Across the period the proportion of patients receiving a second Allo-HSCT where time from start of therapy to occurrence of 1st relapse (PFS1)>12 months was 67% with year-on-year trends.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of second allogeneic haematopoietic stem cell transplant to treat relapsed disease for all ages

Whilst the evidence review focused on adults, second Allo-HSCT for relapsed disease are a relevant treatment option for children. Data from the British Society for Blood and Marrow Transplantation (BSBMT) demonstrates that outcomes following HSCT are generally superior in children to those in adults across all indications. On this basis, extrapolating from the evidence for second transplant for relapse disease in adults, this commissioning position in relation to second transplants for relapsed disease applies to patients of all ages.

Evidence review summary

1. Is allogeneic haematopoietic stem cell transplant clinically effective in the treatment of adult patients with haematological malignancy who have relapsed following an initial allogeneic transplant?

Published evidence of clinical effectiveness is limited to retrospective case series and two controlled studies. These are mostly single centre and report outcomes on patients treated over periods of more than twenty years, during which time approaches to treatment and options available may have varied. Risks of bias and confounding are inherent in the study design. The patients reported in these studies are heterogeneous with respect to disease, disease stage, previous treatment, conditioning regimes as well as demographic factors (age, gender, etc.). The outcomes reported from these studies indicate a 5-year overall survival from Allo-HSCT as a second transplant of 16% to 28%. Non-relapse mortality was reported as 18 to 63% over periods varying from 100 days to 5 years.

2. Is allogeneic haematopoietic stem cell transplant cost effective in the treatment of adult patients with haematological malignancy who have relapsed following an initial allogeneic transplant?

The review found a study indicating the cost of second HSCTs at a hospital in the United States, but it did not report the cost effectiveness of the procedure.

3. Is there any evidence to indicate the comparative effectiveness of Allo-HSCT compared to other management strategies in adult patients who have relapsed following an initial allogeneic transplant?

The review found one study of the comparative effectiveness of Allo-HSCT compared to other management strategies in patients who have relapsed following an initial transplant for haematological malignancy. It reported no significant difference in one-year survival rates between people with acute myeloid leukaemia and myelodysplastic syndrome treated with supportive care, palliative or intensive chemotherapy, a second Allo-HSCT or other treatments. The only factor influencing overall survival was time to relapse after first Allo-HSCT.

4. Is it possible to specify selection criteria which would enable the identification of those patients relapsing after an initial transplant who are most likely to have a favourable outcome from an Allo-HSCT?

Univariate regression analysis in four studies suggested that longer time interval between first transplant and relapse (>1 year vs <1 year) is associated with better survival. One study also suggested that younger age (<40 years vs. >40 years) at time of 2nd transplant and disease stage at second transplant (early versus advanced) may also be associated with better survival. Another study reported that longer survival was associated with longer duration of remission after first Allo-HSCT, with lower stage at second HSCT and with a related first HSCT. A further study reported better outcomes in patients in remission at second transplant, with an interval from first transplant to relapse of more than ten months and those who received total body irradiation.

Supplementary evidence

A retrospective cohort study of 116 patients with acute myeloid leukaemia (AML), myelodysplastic syndromes and myeloproliferative disorders who underwent a second Allo-HSCT for disease relapse was accepted for publication in a peer reviewed journal in December 2015. (Orti G., et al.). At the time of second transplant 80 patients (70%) had active disease, and 28 (25%) were in complete remission.

Overall 5 year survival was 32% (SE 4.7%). In multivariable regression 3 factors were adversely associated with outcome survival: active disease at time of second transplant, time from first to second transplant less than 430 days, and donor other than an HLA matched sibling. Disease-free survival at 5 years was 30%, and 5 year non-relapse mortality was 32%. 47% of patients developed acute graft versus host disease (GvHD) and 32% developed chronic GvHD.

Comparison of overall survival between first and second transplant

Data from the BSBMT database for the period 2007-2012, included in its report to commissioners (BSBMT 6th Report to Specialist Commissioners), were reviewed. These indicated that: survival outcomes for allogeneic transplants using matched unrelated donors are nearly as good as those using sibling donors; five year overall survival of c.30% is comparable with the outcomes of first transplant for some subgroups of acute leukaemia and outcomes for children are better than adults

6 Criteria for Commissioning

Indications and contra-indications

Patients whose first Allo-HSCT results in relapse can be considered for a second allogeneic transplant, where the following criteria are met:

(i) Patient is in complete remission

(ii) Patient relapses >12 months after first Allo-HSCT

(iii) Patient is clinically fit to undergo treatment (as determined by MDT - see governance for more detail)

Second Allo-HSCT for relapse disease for patients meeting these criteria will be routinely commissioned.

Exclusions

Patients whose first Allo-HSCT results in relapse should not be considered for a second treatment, where:

(i) Patient relapse occurs <12 months after first Allo-HSCT

No patients should be offered a further Allo-HSCT if their second results in relapse.

Second Allo-HSCT for relapse disease for patients meeting these criteria will **not** be routinely commissioned.

7 Patient Pathway

When patients relapse following their first Allo-HSCT, a multi-disciplinary team consisting of a haematology specialist, specialist nurse and transplant physicians is called to assess clinical options. These include: further chemotherapy; withdrawal of immunosuppressive treatment (given to reduce graft-versus-host disease); infusion of donor lymphocytes; treatment with cytokines; or a second Allo-HSCT. Where relapse has occurred >12 months after procedure, a decision whether the patient is clinically fit to undergo a second Allo-HSCT is taken. Decision making about this and other treatments must involve the patient. Sufficient information must be provided to enable the patient to understand the potential risks and benefits of the treatment and make an informed decision about their treatment options.

Where a decision to go ahead with a second Allo-HSCT is taken, the procedure is similar to that of the first. The transplant procedure begins with ‘conditioning’ therapy (chemotherapy with or without total body irradiation) at a range of doses depending on the type and severity of disease being treated. The aim of conditioning is to:

1. Eradicate the host immune response, to minimise graft rejection
2. Kill leukaemia/tumour cells (in malignant diseases)
3. Eradicate existing bone marrow tissue (in order to provide space for engraftment of transplanted donor stem cells)

The patient pathway is described in detail in the BMT service specifications for adultsB04/S/a and children B04/S/b– (see Section 12: Documents that have informed this policy proposition for further detail).

8 Governance Arrangements

The governance arrangements are described in detail in the BMT service specifications for adults. All providers of Allo-HSCT must have the appropriate level of Joint Accreditation Committee- ISCT & EBMT (JACIE) accreditation.

Decision on patient treatment to be undertaken by multi-disciplinary team consisting of haematology specialist, specialist nurse and transplant physicians.

Bone marrow, peripheral blood stem cells, or umbilical cord blood stem cells may be used as donor stem cell sources. Use of umbilical cord cells must be in line with the UK Cord Blood Working Group Recommendations for donor selection. Use of double cord units must be notified in advance to the commissioner in view of the likely increased costs and to ensure the selection protocol has been followed.

9 Mechanism for Funding

Funding for stem cell transplantation is through the NHS England teams responsible for specialised commissioning. The funding arrangements are described in detail in the BMT service specifications for adults (B04/S/a) and children (B04/S/b) respectively.

10 Audit requirements

Complete data must be submitted to the BSBMT registry for all transplants carried out by centres in England. This will enable better evaluation of clinical outcomes broken down by patient and disease-related variables. All centres must undergo regular JACIE inspection. All centres must provide the data required for the BMT Quality Dashboard. Audit requirements are described in more detail in the BMT service specification.

Outcome data for second allogeneic transplants for relapsed disease must be separately identifiable within the BSBMT database, and specifically included within the annual BSBMT report to commissioners.

11 Documents that have informed this policy

Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised (January 2015). Reference: NHS England B04/P/a
BMT Service Specifications for adults, B04/S/a and children B04/S/b

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

Carlens S, Ringden O, Aschan J et al. Risk factors in bone marrow transplant recipients with leukaemia. Increase relapse risk in patients treated with ciprofloxacin for gut decontamination. *Clinical transplantation* 1998; 122; 84-92.

Orti G, et al. Outcome of Second Allogeneic Hematopoietic Cell Transplantation after Relapse of Myeloid Malignancies following Allogeneic Hematopoietic Cell Transplantation: A Retrospective Cohort on Behalf of the Grupo Español de Trasplante Hematopoyetico. Biol Blood Marrow Transplant. 2016 Mar;22(3):584-8.