NHS England

Clinical commissioning policy: Haematopoietic Stem Cell Transplantation (HSCT) for Lymphoplasmacytic Lymphoma (Adults)

Reference: NHS England F01X01/01

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Clinical Commissioning Policy Proposition: Haematopoietic Stem Cell Transplantation (HSCT) for Lymphoplasmacytic Lymphoma (Adults)

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Plain Language Summary

Lymphoplasmacytic Lymphoma is a rare form of slow growing non-Hodgkin Lymphoma (NHL). It occurs when a type of white blood cell, called plasma cells, become abnormal and grow out of control. The abnormal plasma cells build up in the bone marrow and sometimes in the lymph nodes, spleen and other organs. They make large amounts of a protein called IgM, which can make the blood thicker than normal.

Haematopoietic stem cell transplantation is also known as blood and marrow transplantation (BMT). It is used to treat a wide spectrum of disorders. It is broadly divided into two main groups: autologous and allogeneic transplantation.

Allogeneic haematopoietic stem cell transplantation (HSCT) is used to treat carefully selected patients with a range of malignant and non-malignant blood-related 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.

Autologous transplantation uses the patient's own stem cells, which are harvested prior to high-dose therapy. It enables the patient to be treated with doses of chemotherapy which are higher than would be possible without subsequent replacement of the harvested cells, because the therapy destroys the patient’s remaining stem cell tissue.

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission haematopoietic stem cell transplantation for lymphoplasmacytic lymphoma in adults.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission haematopoietic stem cell transplantation for lymphoplasmacytic lymphoma in adults.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether the proposed additional indications for haematopoietic stem cell transplantation for lymphoplasmacytic lymphoma in adults will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Haematopoietic stem cell transplantation (HSCT), also known as blood and marrow transplantation (BMT) is used to treat wide spectrum of haematological, and increasingly, non-haematological disorders. It is broadly divided into two main groups: autologous and allogeneic transplantation. These are explained in more detail in the next section.

Stem cell transplantation, particularly allogeneic haematopoietic stem cell transplantation (AlloSCT), is a high cost and highly specialised procedure performed by skilled and experienced transplant teams working in specialist centres. Allogeneic transplantation carries a relatively high mortality and morbidity, and these must be weighed against the potential longer-term survival benefits when considering a patient for transplantation. Rigorous patient selection is of paramount importance.

Lymphoplasmacytic Lymphoma is a rare form of slow growing non-Hodgkin Lymphoma (NHL). It occurs when a B-cell lymphoma become abnormal and grow out of control.

This policy document sets out the criteria for which autologous and allogeneic transplants will be commissioned routinely by NHS England for lymphoplasmacytic lymphoma in adults. For a more detailed description of the transplantation services which will be commissioned and the service standards which should be met by transplant centres please refer to the BMT Service Specification.

Second allogeneic transplants for relapsed disease are excluded from this policy. The commissioning of second transplants is defined in the commissioning policy proposition for second haematopoietic stem cell transplant (F01X07).

3. Definitions

Allogeneic haematopoietic stem cell transplantation (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.

Patients require detailed pre-transplant assessment and investigations to assess their clinical status and fitness to proceed to transplant. The transplant procedure begins with 'conditioning' therapy (chemotherapy with or without total body irradiation [TBI]) at a range of doses depending on the type and severity of disease being treated. The aim of conditioning is to:

- Kill tumour cells (in malignant diseases)
- Eradicate existing bone marrow tissue (in order to provide space for engraftment of transplanted donor stem cells)
- Suppress the patient's immune system, so as to minimise the risk of graft rejection

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.

Autologous transplantation uses the patient's own stem cells, which are harvested prior to high-dose therapy. It is performed as part of dose escalation therapy, and it enables the patient to be treated with doses of chemotherapy which are higher than would be possible without subsequent replacement of the harvested cells, because the therapy destroys the patient's remaining stem cell tissue.

Lymphoplasmacytic Lymphoma is a rare form of slow growing non-Hodgkin Lymphoma (NHL). It occurs when a B-cell lymphoma become abnormal and grow out of control. The abnormal plasma cells build up in the bone marrow and sometimes in the lymph nodes, spleen and other organs. They make large amounts of a protein called IgM, which can make the blood thicker than normal.

4. Aim and objectives

This policy aims to:
Specify the criteria for which autologous and allogeneic haematopoietic stem cell transplants will be commissioned routinely by NHS England for adults with lymphoplasmacytic lymphoma.

The objectives are to:

- Optimise patient outcome after autologous and allogeneic stem cell transplantation
- Reduce variation in access to BMT
- Ensure that BMT is commissioned for those conditions for which there is acceptable evidence of clinical benefit and cost-effectiveness
- Promote the cost-effective use of resources

• Reduce unacceptable variation in clinical practice
• Ensure that experimental treatments are offered only in the context of properly conducted research.

5. Epidemiology and needs assessment

Lymphoplasmacytic Lymphoma/Waldenstrom's Macroglobulinaemia is a form of non-Hodgkin Lymphoma (NHL). NHL has an estimated 20 year prevalence of 67,000 in 2014/15 in England (MacMillan, ONS, 2014).

Only a small fraction (less than 2%) of patients diagnosed with NHL every year are registered as having LL/WM worldwide. (Leukemia and Lymphoma Society, 2013). This results in an estimated prevalence of LL/WM in England in 2014/15 of c. 1,200 (or a prevalence rate of c. 2 per 100,000 of the total population living in England).

In 2013, the number of first transplants for lymphoma was 881. This is broken down into 251 Allograft and 630 Autograft transplants (BSBMT Register 2013).

6. Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of haematopoietic stem cell transplantation for lymphoplasmacytic lymphoma in adults defined in the criteria for commissioning section of this document.

This review aimed to address the following research questions:

1. Is there sufficient quality evidence of clinical effectiveness to support new S and CO recommendations for haematopoietic stem cell transplant for Lymphoplasmacytic Lymphoma?

2. Is there any evidence to indicate the comparative effectiveness of HSCT compared to other management strategies for Lymphoplasmacytic Lymphoma?

3. Is there evidence to indicate the cost effectiveness compared to other management strategies?

Part 1: Quality of evidence

Given the rarity of lymphoplasmacytic lymphoma (LL), also known as Waldenstrom's macroglobulinaemia (WM), and the heterogeneous pre-treatment that patients had received prior to haematopoietic stem cell transplantation (HSCT), results from the literature search have been scarce and inconclusive. Studies were mostly retrospective, and often had small patient sample sizes (Caravitas et al., 2009; Dreger et al., 2007). There is a potential risk of selection bias in the studies given

that more immunocompetent and younger patients would be offered transplant. Moreover, there were no randomised controlled trials or systematic reviews conducted to assess HSCT as a treatment for LL. Any policy recommendation will therefore be delivered with these caveats attached.

Autologous vs. Allogeneic

A study with 36 patients favoured autologous HSCT (autoSCT) over allogeneic HSCT (alloSCT) because of the higher overall survival (OS) rates (70% vs. 46% at 3 years) and progression free survival (PFS) rates (65% vs. 31% at 3 years) (Anagnostopoulos et al., 2006).

In 2010, Kyriakou et al. published two retrospective studies with large patient samples using data reported to the European Blood and Bone Marrow Transplantation Group (EBMT) Registry between January 1991 and 2005. The two papers together were used to compare the clinical outcomes of WM patients who had undergone autologous HSCT (158 patients) and allogeneic HSCT (86 patients). One paper (Kyriakou et al., 2010a) showed that autologous stem cell transplant (autoSCT) combined with high dose therapy had low levels of toxicity and an acceptable level of non-relapse mortality (NRM) of 3.8% at 1 year. Overall survival (OS) rates were 68.5% at 5 years, while progression free survival (PFS) was 39.7%. Patients who received autoSCT at VGPR1/PR1 had better outcomes, with PFS at 73% and OS at 77% at 5 years. However, patients who were chemorefractory or had received at least 3 lines of treatment had a significantly inferior PFS and OS, and other prognostic risk factors identified include age of over 50 years and male sex. These findings suggest that autoSCT is most effective for younger patients who receive transplantation at first response. The other paper (Kyriakou et al., 2010b) investigated the effectiveness of allogeneic SCT in the treatment of WM. Overall, NRM at 5 years was at 27%, and the 5-year OS and PFS were 64% and 52%, respectively, but it was not clear how patients who were CR/PR1, CR/PR>1, chemorefractory or primary resistant responded. The study concluded that donations taken from HLA-identical siblings or a matched unrelated donor (MUD) did not result in any statistical difference in NRM. Read together, the two papers support the view that HSCT is effective in triggering a response in WM patients. However, patient selection is of paramount importance. In general, young patients with high-risk WM, as defined by the International Prognostic Scoring System for Waldenström's macroglobulinemia (IPSSWM) appear to have better responses and OS rates. For autoSCT, VGPR1/PR1 patients performed well whereas alloSCT was recommended for chemorefractory, chemoresistant patients and those who have failed autoSCT. In corroboration of this data, Usmani et al. (2011) presented evidence from a 158 patient study on autoSCT to show that post-transplantation, naive patients at 5 years had better PFS than heavily pre-treated patients (76% vs.68%) and OS (49% vs. 41%), though neither of these figures are statistically significant.

Graft-versus-host disease effect in the context of safety

Anagnostopoulos et al. (2006) concluded with a patient sample size of 36 patients that alloSCT also had higher non-relapse mortality rates, at 40% after 3 years, as opposed to 11% for autoSCT. This finding is supported by Gilleece et al. (2008),

who found autoSCT to be a safe treatment, with no transplant-related mortalities (TRM) at 1 year. Dreger et al. (2007) also reported that autoSCT was a safe procedure with 100% OS at a median follow up of 69 months, although the reliability of the data was marred by the small (n=12) patient sample size. The much larger study by Kyriakou et al. (2010b) has similar findings, reporting that alloSCT was more toxic than autoSCT; 5-year NRM was 27% for alloSCT, compared to 5.8% for autoSCT. However, the higher PFS seen in alloSCT patients was attributed to a chronic graft-versus-host disease (GVHD) effect. Curiously, the OS in the alloSCT sample plateaued at a steady 64% at 5 years after transplantation, whereas the same figure in the autoSCT sample dropped from 68.5% to approximately 57% from year 5 to year 8.

Allogeneic transplantation - HLA-identical sibling vs. matched unrelated donor (MUD)

Gileece et al. (2008) had only 1 MUD patient; the endpoint outcomes of HLA-identical vs. MUD donors could therefore not be evaluated. Meanwhile, Kyriakou et al. (2010b) did not find any difference in the NRM of HLA-identical and MUD donors. Other studies reported the number of patients who received HLA-identical sibling or matched unrelated donor (MUD) allografts, but did not explicitly state patient observations or endpoint outcomes. As such, the paucity of evidence makes it impossible to draw a conclusion on the difference in effectiveness between the two types of allografts.

Overall, the data suggests that autoSCT is a safer therapy option compared to alloSCT, and seems to show higher efficacy to patients who are naive or in PR1. AlloSCT, on the other hand, is more toxic but can result in good PFS. However, the fact that most patients undergoing alloSCT were usually more heavily pre-treated or had greater disease severity at the time of transplantation precludes a definitive conclusion.

Part 2: Comparative effectiveness versus other management strategies

Usmani et al. (2011) reported that patients who underwent autoSCT showed better response compared to those who received other types of therapy (21% in CR vs.17%; 67% in PR vs.18%), resulting in higher PFS at 5 years, 69% vs. 41%. OS was similar at 5 years, but OS plateaued and remained high at 78% up until year 12, whereas patients who did not receive a transplant only had an OS of 40% at 12 years.

Part 3: Cost effectiveness

There were no studies specifically addressing the clinical and cost effectiveness of haematopoietic stem cell transplantation for the treatment of Lymphoplasmacytic Lymphoma compared to usual care options such as treatment with nucleoside analogues, alkylating agents and rituximab.

7. Proposed criteria for commissioning

Haematopoietic stem cell transplantation for lymphoplasmacytic lymphoma will be commissioned according to the criteria below.

The use of umbilical cord cells must be in line with the UK Cord Working Group Recommendations for donor selection. Use of double cord must be notified in advance to the commissioner to demonstrate the donor selection protocol has been followed.

Inclusion criteria
Autografts and allografts (sibling or unrelated) will be commissioned for adults with lymphoplasmacytic lymphoma at stage:

- CR/PR>1, OR
- Primary resistant – sensitive to salvage

Exclusion criteria
Bone marrow transplant is not commissioned for any stage of lymphoplasmacytic lymphoma which is not listed in this policy.

Given the nature of this condition and the above criteria, clinicians will be expected to adopt a recognised protocol such as the BSBMT guidelines developed to ensure consistent, evidence based practice across England.

Policy development
Clinical practice continues to evolve, and the commissioning policy will continue to be reviewed regularly and updated to reflect current evidence.

8. Proposed patient pathway

Refer to existing policy for HSCT (NHS England B04/P/a).

9. Proposed governance arrangements

Refer to existing policy for HSCT (NHS England B04/P/a).

10. Proposed mechanism for funding

Refer to existing policy for HSCT (NHS England B04/P/a).

11. Proposed audit requirements

Refer to existing policy for HSCT (NHS England B04/P/a).

12. Documents which have informed this policy proposition

NHS England: Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. Reference: NHS England B04/P/a January 2015

BSBMT Indications for BMT, October 2013

BSBMT Indications for BMT, February 2012

13. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).

The policy for haematopoietic stem cell transplantation (F01X01) is subject to annual revision.