Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) for lymphoplasmacytic lymphoma (adults)

Reference: NHS England: 16067/P

(Note: This policy is an additional indication to policy B04/P/a and should be read in conjunction with that document)

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Clinical Commissioning Policy: Haematopoietic stem cell transplantation (HSCT) for lymphoplasmacytic lymphoma (adults)

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Prepared by NHS England Specialised Services Clinical Reference Group for Blood and Marrow Transplantation

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Contents

Policy Statement

NHS England will commission haematopoietic stem cell transplantation (HSCT) for lymphoplasmacytic lymphoma (adults) in accordance with the criteria outlined in this document. 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 lymphoplasmacytic lymphoma

Lymphoplasmacytic lymphoma is a rare form of slow-growing non-Hodgkin Lymphoma (NHL) - a type of cancer.

- 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.

About current treatments

Patients are usually treated with chemotherapy medicines or a biological medicine called ‘rituximab’.

New treatment

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

- **Autologous** - this uses the patient's own stem cells, which are collected (harvested) before the patient is treated with doses of chemotherapy to remove damaged or diseased cells. The collected cells can then be transplanted back to the patient after treatment.
- **Allogeneic** - this 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. It involves replacing diseased or damaged cells with healthy cells from another person (a donor).

What we have decided

NHS England has carefully reviewed the evidence for haematopoietic stem cell transplantation for the treatment of lymphoplasmacytic lymphoma. We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

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

Haematopoietic stem cell transplantation (HSCT), also known as bone 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, 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 (LL) is a rare form of slow growing non-Hodgkin Lymphoma (NHL). It occurs when 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.

2 Definitions

Allogeneic 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) 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 HSCT 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 or Waldenstrom's Macroglobulinaemia (WM) is a rare form of slow growing NHL. It occurs when a B-cell lymphoma becomes abnormal and grows 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.

3 Aims 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.

4 Epidemiology and Needs Assessment

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 or WM worldwide (Leukaemia 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 6th Report to Specialist Commissioners, 2013).

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of HSCT for LL 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 standard of care (S) and clinical option (can be considered after assessment of risks and benefits) (CO) recommendations for HSCT for LL?
2. Is there any evidence to indicate the comparative effectiveness of HSCT compared to other management strategies for LL?
3. Is there evidence to indicate the cost effectiveness compared to other management strategies?

Quality of evidence

Given the rarity of LL, also known as WM, and the heterogeneous pre-treatment that patients had received prior to 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.

Autologous vs. Allogeneic transplant

A study with 36 patients favoured autologous HSCT over allogeneic HSCT 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 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 HSCT 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. OS rates were 68.5% at 5 years, while PFS was 39.7%. Patients who received autologous HSCT 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 an inferior PFS and OS, and other prognostic risk factors identified include age of over 50 years and male sex. These findings suggest that autologous HSCT is most effective for younger patients who receive transplantation at first response. The other paper (Kyriakou et al., 2010b) investigated the effectiveness of allogeneic HSCT 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 human leukocyte antigen (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 autologous HSCT, VGPR1/PR1 patients performed well whereas allogeneic HSCT was recommended for chemorefractory, chemoresistant patients and those who have failed autologous HSCT. In corroboration of this data, Usmani et al. (2011) presented evidence from a 158 patient study on autologous HSCT 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 allogeneic HSCT also had higher non-relapse mortality rates, at 40% after 3 years, as opposed to 11% for autologous HSCT. This finding is supported by Gilleece et al. (2008), who found autologous HSCT to be a safe treatment, with no transplant-related mortalities (TRM) at 1 year. Dreger et al. (2007) also reported that autologous HSCT was a safe procedure with 100% OS at a median follow up of 69 months, although the reliability of the data was marred by patient sample size (n=12). The much larger study by Kyriakou et al. (2010b) has similar findings, reporting that allogeneic HSCT was more toxic than autologous HSCT; 5-year NRM was 27% for allogeneic HSCT, compared to 5.8% for autologous HSCT. However, the higher PFS seen in allogeneic HSCT patients was attributed to a chronic graft-versus-host disease (GVHD) effect. Curiously, the OS in the allogeneic HSCT sample plateaued at a steady 64% at 5 years after transplantation, whereas the same figure in the autologous HSCT sample dropped from 68.5% to approximately 57% from year 5 to year 8.

Allogeneic transplantation – Human Leukocyte Antigen (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 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 autologous HSCT is a safer therapy option compared to allogeneic HSCT, and seems to show higher efficacy to patients who are naive or in PR1. Allogeneic HSCT, on the other hand, is more toxic but can result in good PFS. However, the fact that most patients undergoing allogeneic HSCT were usually more heavily pre-treated or had greater disease severity at the time of transplantation precludes a definitive conclusion.

Comparative effectiveness versus other management strategies

Usmani et al. (2011) reported that patients who underwent autologous HSCT 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.

Cost effectiveness

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

6 Criteria for Commissioning

HSCT for LL 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

HSCT is not commissioned for any stage of LL 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.

7 Patient Pathway

Refer to NHS England Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation B04/P/a.

8 Governance Arrangements

Refer to NHS England Clinical Commissioning Policy Haematopoietic Stem Cell Transplantation (NHS England B04/P/a).

9 Mechanism for Funding

Refer to NHS England Clinical Commissioning Policy Haematopoietic Stem Cell Transplantation (NHS England B04/P/a).

10 Audit Requirements

Refer to NHS England Clinical Commissioning Policy Haematopoietic Stem Cell Transplantation (NHS England B04/P/a).

11 Documents which have informed this Policy

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 in relation to LL, October 2013

BSBMT Indications for BMT, February 2012

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision. As an additional indication for HSCT, the content of this policy may be incorporated into the overarching NHS England policy document for HSCT.

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