Clinical Commissioning Policy: Use of plerixafor for stem cell mobilisation (updated to include paediatrics)

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Clinical Commissioning Policy: Use of plerixafor for stem cell mobilisation (update to include paediatrics)

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Prepared by NHS England Specialised Services Clinical Reference Group for Paediatric cancer services

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Policy Statement

NHS England will commission plerixafor for stem cell mobilisation for children and young people with lymphomas and paediatric-type solid malignant tumours 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 the current treatment

Patients with cancers such as

- myeloma - a cancer that affects the bone marrow;
- lymphoma - a cancer that affects cells of the immune system called 'lymphocytes'
- paediatric-type solid malignant tumours - cancerous tumours; can be successfully treated with chemotherapy followed by transplantation of blood stem cells.

For some children, treatment does not go ahead as it is not possible to collect enough cells. A second attempt to collect these cells can be tried, however it requires a hospital stay and the use of stronger chemotherapy. This can lead to side effects.

About the new treatment

A medicine called plerixafor can be used without chemotherapy in a second attempt at collecting the stem cells.

- This has been shown to be highly effective.
- The treatment can also be safely given to a patient as an outpatient, i.e. without a hospital stay.

In addition, if patients have 'indicators' that highlight that the collection might fail, they can be given plerixafor before treatment starts. This aims to prevent patients from having a collection failure in the first place.

What we have decided

NHS England has carefully reviewed the evidence for the use of plerixafor for stem cell collection in children and young adults with lymphomas and paediatric-type solid malignant tumours and has concluded that there is enough evidence to consider making the treatment available for this group.

1 Introduction

NHS England already routinely commissions plerixafor for stem cell mobilisation in adults and children with Hodgkin's Disease (HD), Non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). This document provides an update to the existing Clinical Commissioning Policy "Use of Plerixafor for Stem Cell Mobilisation (Update)" (Ref: NHS England B04/P/b) to include children, young people and young adults (≤24 years) with lymphomas and paediatric-type solid malignant tumours and describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission plerixafor for these patients.

This document also updates the proposed criteria for commissioning, proposed governance arrangements and proposed audit requirements.

Patients with Multiple Myeloma (MM), Hodgkin's Disease (HD), Non-Hodgkin's Lymphoma (NHL) and children, young people and young adults (≤24 years) with lymphomas and paediatric-type solid malignant tumours may be successfully treated with high dose chemotherapy followed by autologous transplantation of peripheral blood stem cells (PBSC). This is standard treatment for certain groups of patients with these disorders and is in accordance with local and national guidance (BSBMT Indications Table 2012). Plerixafor is licensed to treat adult patients (>18 years) for the collection of stem cells prior to autologous transplantation of PBSC (EMA license EMA/H/C/1030).

Prior to the autologous transplant a 'mobilisation' procedure is required to increase the number of circulating PBSC in the blood compared to the resting state. These circulating PBSC can then be collected using a cell separator using a procedure called apheresis. Current mobilisation protocols combine the use of intravenous chemotherapy with administration of a growth factor called G-CSF which, when combined, results in successful mobilisation and collection of PBSC in approximately 80% of patients. About 10 -20% of the above patients fail to collect enough cells to proceed to the autologous transplant. Usually in order to proceed to the planned transplant, these patients are offered a second round of stem cell mobilisation and stem cell collection using a more intensive chemotherapy approach which requires a further inpatient admission, additional chemotherapy and G-CSF costs and has

associated toxicity (e.g. prolonged cytopenias, infections etc.) Additional attempts at mobilisation are only effective in a small number of patients (up to 20%). Mobilisation in children can often be particularly challenging due to the intensity of chemo-radiotherapy regimes received earlier in the treatment pathway, and the increasing use of sequential high–dose therapy.

The recent introduction of plerixafor combined with G-CSF has been shown to increase the PBSC yield and can result in successful mobilisation of PBSC in up to 80% of patients who have previously failed to collect sufficient cells (rescue treatment). In addition, when plerixafor is administered following chemotherapy and G-CSF in patients with a low level of circulating stem cells in the blood on the predicted day of collection, it can enhance the number of stem cells mobilising into the blood and avoid a failure of PBSC harvesting (pre-emptive treatment). This then avoids the need for a second attempt at mobilisation. The use of plerixafor avoids the cost of further hospital bed days and the additional G-CSF and chemotherapy administration, avoids the toxicity and complications of the more intensive chemotherapy treatment and allows patients to move forward to their proposed transplant more quickly which can be critical in preventing disease progression prior to the planned transplant.

2 Definitions

Stem Cell Mobilisation – this means the successful increase in the number of stem cells (PBSC) circulating in the blood from where they can be collected.

Stem Cell Harvest – this means the collection of the stem cells (PBSC) from the blood using a cell separator machine.

Solid tumours – this means an abnormal mass of tissue. Solid tumours may be benign (not cancer), or malignant (cancer). Different types of solid tumours are named for the type of cells that form them. Examples of solid tumours are sarcomas, carcinomas, and lymphomas. Leukaemias (cancers of the bone marrow and blood) generally do not form solid tumours.

Apheresis – this is the name given to the flow of the patient's blood through the cell separator during which the stem cells (PBSC) are separated and collected into a separate container in which they can then be frozen for later use.

CD34+ cell – this is the protein expressed on the stem cells (PBSC) that we can detect allowing us to count the number of stem cells in the blood or the harvest.

Target dose – optimal number of PBSC (CD34+ cells) required to safely proceed to a transplant.

Autologous stem cell transplant – this is the process of high dose chemotherapy followed by infusion of the harvested stem cells which will repopulate the bone marrow and allow the recovery of the patient's blood counts.

3 Aims and Objectives

This policy aims to:

- Identify which patients are suitable for the use of plerixafor to augment stem cell mobilisation and collection.

The objectives are to:

- Reduce the number of patients failing stem cell mobilisation who have to undergo further attempts at stem cell mobilisation using more intensive chemotherapy.
- Reduce the number of patients who are unable to have the planned autologous stem cell transplant due to insufficient stem cells being collected. Currently these patients may either be ineligible for a transplant procedure which may negatively impacting on their survival, or alternatively may instead have to undergo allogeneic transplantation which is a more complex procedure with higher costs and morbidity.

4 Epidemiology and Needs Assessment

Approximately 10-20% of patients undergoing stem cell mobilisation fail to collect an adequate number of stem cells to proceed to stem cell transplant at the first attempt.

These patients would be eligible for either rescue or pre-emptive treatment with plerixafor.

Data from Nottingham and Glasgow show that approximately 16% of patients will require pre-emptive plerixafor, of which > 90% can then successfully be mobilised following intervention with pre-emptive plerixafor, preventing the requirement for second mobilisation attempt (data not published).

5 Evidence base

Evidence base for the use of plerixafor with HD, NHL or MM:

Plerixafor (Mozobil, AMD3100) is a potent, selective and transient antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell–derived factor-1 (SDF-1), also known as CXCL12. It mobilises stem cells from the bone marrow increasing their number in peripheral blood. Unlike G-CSF, plerixafor is not a growth factor but works alongside G-CSF to release cells more efficiently (Uy et al 2008, Puisc et al 2008, Rosenkilde et al 2004). This drug was introduced into the UK in August 2009.

Plerixafor has been used in a variety of settings. However, this policy focuses only on the use of plerixafor in two settings: 1) after a failed prior mobilisation (rescue mobilisation), 2) for mobilisation in patients with ongoing low CD34+ cell counts to prevent a mobilisation and collection failure (pre-emptive use).

There is Randomised Control Trial (RCT) data to suggest that plerixafor combined with G-CSF is superior to G-CSF alone as a first mobilisation strategy, but in the UK chemotherapy plus G-CSF is the standard mobilisation regimen and in view of the cost of plerixafor, this policy is only concerned with patients who have failed or are failing stem cell mobilisation. Upfront use of plerixafor is not being considered or recommended.

Evidence for Plerixafor following Mobilisation Failure

On average, up to 20% of patients undergoing standard mobilisation attempts fail to reach the accepted minimum of 2×10^6 CD34+ cells/kg of the patient's body weight (Hubel at al, 2011, Jantunen et al 2008). The definition for difficult-to-mobilise patients varies but in general includes the following characteristics:

- peripheral blood CD34+ cell counts are low ($<10 \times 10^6$/L in many centres)
- minimal collection target ($>2 \times 10^6$ CD34+ cells/kg) is not achieved with a single mobilisation

Remobilisation is a viable option in patients who have failed mobilisation with the first attempt or in whom a suboptimal graft has been collected. Historically, chemotherapy-based remobilisation has been often advocated in patients who have failed a first mobilisation (Arcaini et al 2011). In a recent single-centre series using predominantly G-CSF for mobilisation (>90% of cases), the success rate of a remobilisation was only 23% as a whole (Rosenkilde et al 2004). Failure rates were 73.5% in patients remobilised with chemotherapy plus G-CSF, 81.6% in patients remobilised with growth factor alone but only 27.8% in patients mobilised with G-CSF plus plerixafor.

Plerixafor combined with G-CSF has significantly increased the efficacy of remobilisation in patients who have failed a previous mobilisation attempt with a success rate of greater than 60% (Jantunen et al 2010). In a compassionate-use study of 115 patients who had failed a previous mobilisation, the success rate ($>2 \times 10^6$/kg CD34+ cells collected) of G-CSF plus plerixafor was 60.3% for NHL, 71.4% for MM and 76.5% for HL, respectively (Calandra et al 2008). Similarly, in an EU compassionate-use series, combination of G-CSF and plerixafor gave successful collections in 75% of patients who had failed a previous mobilisation (Duarte et al 2010).

Most of these patients achieved a timely and stable engraftment with rare and/or manageable side effects (Hubel et al 2011, Arcaini et al 2011, Calandra et al 2008).

Evidence for Pre-Emptive Plerixafor

The use of plerixafor in conjunction with chemotherapy and G-CSF to salvage a mobilisation failure is now being increasingly used. Existing published results indicate that the combination is safe and effective. Peripheral blood CD34+ cell counts are increased several-fold in more than 90% of patients to allow collection of the target yield (Hubel et al 2011, Calandra et al 2008). In one study, patients failing mobilisation with chemotherapy plus G-CSF achieved a 2.7-fold increase in median hematopoietic progenitor cell (HPC) product concentration after plerixafor was added.

A further study showed PBSC collection data of 38 consecutive patients with lymphoma (Hodgkin's and non-Hodgkin's) and MM who underwent chemo-mobilisation and high-dose G-CSF and just-in-time plerixafor in order to evaluate the efficacy of this treatment combination. All patients with MM and all but one patient with lymphoma (95% of total patients) collected the minimum required number of CD34+ cells to proceed with autologous stem cell transplantation (>2 × 106/kilogram of body weight) (Smith et al 2013).

Cost-Effectiveness

Plerixafor is a high cost drug, costing £4883 per vial plus VAT.

Cost analyses have been performed by multiple groups and some studies have claimed a cost saving by using plerixafor (Arcaini et al 2011, Vishnu et al 2011), while other studies have shown an increase in cost that may be justified by fewer apheresis sessions and a greater likelihood of collecting enough stem cells to proceed to transplantation (Arcaini et al 2011).

The Scottish Medicines Consortium reviewed and approved plerixafor for use in NHS Scotland within its licensed indications (NHS Scotland 2009). The manufacturer presented a cost-utility analysis of the use of plerixafor for mobilisation in MM and NHL patients who had failed at least one previous mobilisation attempt. The comparator mobilisation treatments were G-CSF and GCSF in combination with cyclophosphamide.

Rates of successful mobilisation were drawn from a range of sources, data from the compassionate use programme being used for plerixafor while a retrospective

analysis was used for G-CSF and G-CSF + cyclophosphamide. Successful mobilisation was followed by autologous transplantation, while those not mobilising were largely assumed to undergo chemotherapy. The effectiveness, survival estimates and utility estimates for these were taken from the literature. Adverse events during mobilisation were not considered.

The key results in MM patients were as follows:

- The cost per successful mobilisation gained was £12,768 compared to G-CSF
- The cost per successful mobilisation gained was £11,074 compared to G-CSF + cyclophosphamide
- A gain of 0.47 quality-adjusted life year (QALY) is at a cost of £18,832 compared to G-CSF, to yield a cost per QALY of £39,649
- A gain of 0.41 QALYs at a cost of £15,561compared to G-CSF + cyclophosphamide, to yield a cost per QALY of £38,278.
- The key results in NHL patients were as follows:
- The cost per successful mobilisation gained was the same as among multiple myeloma patients
- A gain of 1.22 QALYs at a cost of £23,950 compared to G-CSF, to yield a cost per QALY of £19,586
- A gain of 1.06 QALYs at a cost of £20,054 compared to G-CSF + cyclophosphamide, to yield a cost per QALY of £18,874 compared to G-CSF + cyclophosphamide.

Most cost-effectiveness studies have not fully captured the variables needed to justify its use, including the cost of delayed transplant which would include

- additional cycles of chemotherapy including inpatient bed days
- increased risk of relapse
- neutropenic fevers requiring further treatment.

In June 2010, the London Cancer New Drugs Group (London Cancer New Drugs Group 2010) estimated that treating a patient with plerixafor cost £10 - £20K per patient. They calculated the additional cost for the drug per 100,000 population to be £8906 (excluding VAT), although clinical opinion suggests that lower dosing may reduce this cost further.

Post-transplant costs may be different when plerixafor is used and these costs have not yet been estimated. For example, plerixafor may mobilise more lymphocytes and lymphocyte precursors in the product, which may result in better outcomes.

A study by Shaughnessy and colleagues (Shaughnessey et al 2011) suggests that the cost of remobilisation with plerixafor and GCSF and chemo mobilisation (intensive chemotherapy and GCSF) are similar once the cost of hospitalisation is considered.

The average number of bed days saved for a further course of mobilising chemotherapy would be 5 days. In addition another advantage of plerixafor is that the toxicity of chemotherapy can often be avoided such as reduced admissions with neutropenic sepsis (currently over 20% of patients receiving chemo-mobilisation) and the need for blood products. The use of plerixafor pre-emptively to avoid mobilisation failure also reduces the cost of bed days required for another cycle of mobilising chemotherapy and further GCSF costs.

Plerixafor has been shown to cause less mobilisation and collection failures and can mobilise patients who have failed a prior mobilisation attempt, allowing more patients to proceed to transplantation, improving the patient experience. Furthermore the collection of PBSC following plerixafor is highly predictable making it highly convenient for patients and collection centres alike.

Prior to the instigation of national commissioning, plerixafor was in use in many transplant centres throughout England, either through prior approval for specified indications or via Individual Funding Requests (IFRs). The aim of this policy is to make access to the drug equitable across the country for the specific groups of patients indicated.

In summary, in patients failing mobilisation, further attempts at mobilisation increase the cost of the procedure whatever option is used. The cost of the use of plerixafor can be considered against other options of high intensity chemotherapy or allograft transplant. The proportion of patients failing mobilisation is constant at up to 20% and the number of patients affected is unchanged whether rescue or pre-emptive use is considered. The greater success of plerixafor in achieving sufficient mobilisation means that more eligible patients will be able to proceed to transplant.

Safety

Plerixafor is well tolerated with few adverse events. Common adverse effects include diarrhoea, injection site erythema, perioral numbness, sinus tachycardia, headache, nausea, abdominal distention, and injection site pain. It does not cause neutropenia or other cytopaenias.

Evidence base specifically for children, young people and young adults (≤24 years) with lymphomas and paediatric-type solid malignant tumours:

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of plerixafor for stem cell mobilisation in children, young people and young adults (≤24 years) with lymphomas and paediatric-type solid malignant tumours.

While it is acknowledged that there is no level 1 evidence for the use of plerixafor in patients with these specific diagnoses, there is strong rationale for commissioning this treatment for the following reasons:

- Plerixafor is used to aid successful mobilisation of the cells and is therefore not dependent directly on specific cancer diagnosis;
- Plerixafor is currently being successfully used in several Principal treatment Centres in England (Aabideen et al 2011);
- From a biological perspective, the evidence considered for the routine commissioning of plerixafor in both adults and children with HD, NHL or MM (see the evidence base for these cohorts, below) supports its use in these population groups – it should therefore be equally applied to patients with other paediatric-type solid malignant tumours;
- A successful stem cell mobilisation enables the administration of a potentially curative high dose chemotherapy; and
- Whilst level 1 evidence in this group is limited, it is recognised that in the low level evidence that does exist it has shown plerixafor to be successful in the collection of stem cells.

Evidence on whether plerixafor in stem cell mobilisation is clinically effective in ensuring adequate stem cell mobilisation and a successful harvest in children with paediatric-type solid malignant tumours where peripheral stem

cell support (PBSCT) is a recognised treatment compared with no intervention or with other standardised treatments

We found no systematic reviews or controlled study evidence on the effects of plerixafor, used in combination with G-CSF, as PBSC mobilisation in children undergoing PBSCT for solid tumours. One randomised study is ongoing and another study is planned, but not yet recruiting.

Most of the supporting data are weak and based on case series reviews (4, 16-26). Although they reported high rates of successful mobilisation and stem cell harvest (50 to 100 percent of patients), the studies were uncontrolled, involved too few patients with too much heterogeneity in patient population to give a fair assessment of the efficacy of this approach. Being case series, they could have exaggerated the absolute effects of this treatment.

Limited data shows that plerixafor may be an effective and safe agent for stem cell collection in paediatric patients with solid tumours (Hubel et al 2011, Aabidden et al 2011, Avramova et al 2011 Emir et al 2014, Hong et al 2012, Maschan et al 2015, Modak et al 2012, Patel et al 2015, Sevilla et al 2012, Son et al 2013, Vettenranta et al 2012), but randomised comparative studies are required to address its efficacy and safety.

Plerixafor appeared to be fairly well tolerated in most of the studies (4, 16-26). However, psychiatric side effects were higher than expected in one of these studies (Son et al). Until more is known from prospective controlled trials, plerixafor should be used with caution in children.

Evidence on whether plerixafor in stem cell mobilisation is cost effective in children with paediatric-type solid malignant tumours where PBSCT is a recognised treatment

We found no studies on the cost-effectiveness of plerixafor in children undergoing PBSCT for solid tumours.

6 Criteria for Commissioning

Patient selection

Patients eligible for treatment with plerixafor are those with Hodgkin's Disease (HD) Non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and children, young people and young adults (≤24 years) with lymphomas and paediatric-type solid malignant tumours who meet the standard criteria and are scheduled for an autologous haematopoietic stem cell transplant but:

1. have failed one previous attempt at mobilisation using a standard mobilisation regimen combining chemotherapy + G-CSF or G-CSF alone (rescue treatment). These patients will be offered a second mobilisation attempt with planned use of combination high dose G-CSF and plerixafor

   or

2. while undergoing mobilisation with a standard chemotherapy + G-CSF or G-CSF based regimen, have a low peripheral blood CD34+ cell count on the day of expected harvest and are not considered by the transplant consultant to have a reasonable chance of collecting enough cells (pre-emptive treatment). These patients will be given plerixafor as an unplanned addition to their mobilisation regimen.

Starting and Stopping Criteria

1) Patients who have previously failed a mobilisation attempt (rescue) should receive G-CSF (10 µg/kg, or in accordance with protocol) subcutaneously each day for 4 consecutive days (It is usually prescribed to the nearest ampoule size multiple, in accordance with transplant centre policy):

- On the fourth day patients assessed as requiring plerixafor (usually if the peripheral blood CD34+ cell number are < 15 per microlitre) receive a dose of 240 µg/kg in the early evening as a subcutaneous injection into the abdomen (as per EMA license EMA/H/C/1030).
- On the morning of the fifth day, a full blood count and peripheral CD34 count should be performed prior to harvest. It is the responsibility of the Transplant

Consultant, to decide whether the harvest should proceed on the basis of the blood CD34+ estimation (usually if above 10 CD34+ cells per microlitre).

- If the count is insufficient to harvest cells that day, or if insufficient stem cells have been harvested, then patients should receive a further dose of GCSF and a repeat dose of plerixafor (240 µg/kg) that evening in an identical fashion to the day before. A second attempt at harvest should be made the following day.

2) Patients who appear to be failing a mobilisation attempt (pre-emptive) – these are patients in whom the CD34+ cell count in the blood is < 15 per microlitre on the day of predicted day of stem cell harvest.

- These patients are given a dose of subcutaneous plerixafor with GCSF 10 µg/kg and an attempt at harvesting is made the following day if the repeat CD34+ is sufficient.
- If the CD34 level in the blood remains < 15 per microlitre then the harvest should be delayed and a further dose of G-CSF and plerixafor may be given that evening.

Stopping Criteria

- A maximum of three doses of plerixafor in total may be used.
- In general a collection totalling >2 X (10^6) CD34+ cells per kilogram body weight will be sufficient to adequately support a single high-dose therapy procedure in adults. Paediatric requirements may differ – clinicians should refer to individual treatment protocols.

Exclusions

- Plerixafor should not be used in pregnant patients, and both male and female patients who are sexually active should be advised to use suitable contraception for three months during and after its use because of the potential harmful effects on the gametes (sperm / ova) and any resulting pregnancy.
- Plerixafor is not funded for patients undergoing a first attempt at stem cell mobilisation unless they meet the criteria for pre-emptive therapy.

- Plerixafor should not be used for patients who have already received it pre-emptively during a previous failed attempt at mobilisation.

7 Patient Pathway

Patients for stem cell harvesting will normally be referred to the stem cell collection unit by the transplant team with a written prescription detailing the target stem cell dose required as per JACIE and Human Tissue Authority (HTA) recommendations. Either the transplant team or the collection team (depending on local factors) will be responsible for the authorisation and administration of plerixafor for patients requiring this intervention. There will be no change to existing arrangements following approval of this policy.

8 Governance Arrangements

- Consent, patient evaluation and investigations prior to the commencement of the mobilisation procedure must be carried out at the stem cell collection centre in accordance with relevant transplant centre policy.
- No additional investigations are required for the provision of plerixafor.
- All processes involved in the provision of plerixafor and the subsequent harvesting of peripheral blood stem cells must fulfil Human Tissue Authority (HTA) requirements and must meet JACIE accreditation standards.
- Use of plerixafor must also be subject to internal provider governance arrangements

9 Mechanism for Funding

From April 2013 NHS England is the responsible commissioner for stem cell transplant. Monitoring of the use of plerixafor in accordance with this policy will be expected in the form of audit data.

10 Audit Requirements

Regular audit should be carried out on the use of plerixafor. Audit criteria will encompass the following:

- % of total patients undergoing mobilisation who require plerixafor
- Number of doses of plerixafor used per patient
- Total CD34+ cells mobilised or sufficient CFU (colony forming units) following plerixafor
- Number of collection days required to obtain sufficient cells for indicated PBSCT
- Time to neutrophil and platelet engraftment following PBSCT to assess the quality of the stem cell harvested.
- Serious unexpected side effects

11 Documents which have informed this Policy

European Public Assessment Report EMA/H/C/1030

12 Date of Review

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

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