Clinical Commissioning Policy

Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation (all ages)

Summary

Treatments for Graft versus Host Disease (GvHD) following haematopoietic Stem Cell transplantation are recommended to be available as routine commissioning treatment options within the criteria set out in this document.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety and/or it is not recommended through the licence authorisation process to be used in those age groups not included in the policy.

Committee discussion

The Clinical Priorities Advisory Group committee papers can be accessed here: www.england.nhs.uk/publication/treatments-for-graft-versus-host-disease-gvhd-following-haematopoietic/

What we have decided

NHS England has carefully reviewed the evidence to treat GvHD following Haematopoietic Stem Cell Transplantation. We have concluded that there is enough evidence to make the following treatments available at this time:

Acute: Extracorporeal photopheresis (ECP)

Chronic: After two or more systemic treatments in those 12 years and over, belumosudil is commissioned, as described by the NICE Technology Appraisal (TA949). For all ages, ECP, pentostatin, rituximab and imatinib may be considered for off-label use. Whilst the clinical evidence is limited and of varying quality, it is recognised that:

- Patients have a high degree of morbidity, particularly those with grade III-IV aGvHD making it difficult to gain consent to participate in clinical trials; and
- The low number of patients who might be suitable for this procedure – across a broad range of indications – means that high quality level 1 evidence is unlikely to become available to support the commissioning position.
- The available evidence is relatively consistent in terms of clinical response rates to treatment. This is particularly the case for ECP.

NHS England has concluded that there is not currently sufficient evidence to support a proposal for the routine commissioning of the following treatments for acute GvHD following HSCT: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells.

Links and updates to other policies

NICE Technology Appraisal (TA949) Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years and over: www.nice.org.uk/guidance/ta949

This document updates:

- Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation (2017)

Plain language summary

About Graft versus Host Disease

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 chemotherapy, with stem cells from a tissue-type matched or mismatched donor. This is called a donor transplant or an allogeneic transplant. It involves replacing diseased or damaged cells with healthy cells from another person (a donor).

- The donor's stem cells contain a type of white blood cell that helps fight infections.
- GvHD happens when these white blood cells (T cells) attack the patient's own tissues.
- This is because the donated cells (the graft) recognise the patient's body cells as foreign tissue.

GvHD is a frequent complication of bone marrow or stem cell transplantation using tissue from another person. GvHD may affect different areas of the patient's body. Most commonly it affects the skin, digestive system (including the stomach and gut) and the liver. GvHD is categorised as acute or chronic and it can occur rapidly soon after transplant (2-3 weeks) or can occur many weeks after and last for months.

The clinical symptoms of GvHD are variable, depending upon the tissues affected.

- Acute GvHD (aGvHD) is characterised by a generalised patchy skin rash, sickness, weight loss, loss of appetite, watery diarrhoea, severe abdominal pain, bloody diarrhoea, and jaundice.
- Chronic (cGvHD) may present with a wider range of symptoms and affect almost any organ, but typically includes symptoms such as alopecia (hair loss), skin thickening and severe rash/erythema of the skin, nail loss, dry mouth and oral lesions, dry eyes, sore muscles and joints, raised liver enzymes, scarring of lung tissue with reduced lung function, pericarditis, and loss of blood cells (red, white, and platelets).

aGvHD is graded in severity from I (mild), II (moderate), III (severe) and IV (very severe) according to the modified Seattle Glucksberg criteria. The grade correlates to survival prognosis with 5-year survival of 25% for grade III and 5% for grade IV disease. (Gratwohl et al, 1995; Cahn et al, 2005).

cGvHD is staged as limited or extensive. cGvHD should be graded as mild, moderate or severe according to the National Institutes of Health (NIH) consensus criteria (Filipovich et al, 2005). Extensive cGvHD causes a great degree of morbidity with loss of health and an increased risk of infection. It can be life limiting.

About treatments for GvHD

Treatment for all GvHD usually starts with steroids. Depending on the type of GvHD, the following treatments may be considered:

- other medicines that reduce the body's immune response (immuno-suppressants)
- a therapy where white blood cells are exposed to UVA light (called 'extracorporeal photopheresis' or ECP)
- a medicine called belumosudil, which works by inhibiting the proteins which are responsible for the potentially life-threatening inflammatory response caused by chronic graft versus host disease.

Epidemiology and needs assessment

In 2022, there were 1,547 allogenic transplants (British Society for Blood and Marrow Transplantation (BSBMT)). The BSBMT Outcomes Register identifies the rate of aGvHD between 34% and 53% (all grades) for all adult allograft recipients depending on stem cell source. Severe Grade 3-4 aGvHD occurs in 7% and 11% of adult and paediatric patients with malignancy indications respectively and in 1% of adults and 5% of paediatric patients with non-malignant indications. Chronic GvHD is reported more commonly following adult allograft procedures. For malignant indications, it occurs at 15% in adults compared to 8% in the paediatric cohort; for non-malignant indications, it occurs at 11% in adults and 8% in paediatrics.

Implementation

aGvHD

NHS England will routinely commission ECP in accordance with the patient pathway for patients meeting the following criteria.

Inclusion criteria

- Patient presents with continued or relapsed clinical features of aGvHD (maculopapular rash; persistent nausea and/or emesis; abdominal cramps with diarrhoea; and a rising serum bilirubin concentration) as determined by clinical examination OR biopsy where disease constellation is not clear; AND
- Is unsuitable for first-line treatment, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of topical therapies, calcineurin inhibitors, systemic corticosteroids, sirolimus and/or mycophenolate mofetil).

Exclusion criteria

Patients who have previously had nil response to the proposed treatment.

Stopping criteria

Patients who do not have a positive response, develop severe toxicity, or for whom the treatment has no effect. Patients must be assessed for efficacy at least every 3 months.

CGvHD

NHS England will routinely commission ECP or the off-label use of pentostatin, rituximab and imatinib in accordance with the patient pathway (see below) for patients meeting the following criteria. After two or more systemic treatments in those 12 years and over, belumosudil can be used according to NICE TA949.

Inclusion criteria

- Patient presents with continued or relapsed clinical features of cGvHD (depends on organ in which it presents e.g. skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration) as determined by clinical examination OR biopsy where disease constellation is not clear; AND
- Is unsuitable for first-line treatment, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of systemic corticosteroids, calcineurin inhibitors and/or sirolimus).

Exclusion criteria

Patients who have contraindications as detailed in the individual product's Summary of Product Characteristics, and / or who have previously had nil response to the proposed treatment.

Stopping criteria

Patients who do not have a positive response, develop severe toxicity, or for whom the treatment has no effect. Patients must be assessed for efficacy at least every 3 months.

Patient pathway

Patients present with symptoms of either acute or chronic GvHD following allogeneic HSCT. A clinical diagnosis is established with the help of biopsy where the classical constellation of symptoms is not present. Where, at clinical diagnosis, patients present with signs or symptoms of acute or chronic GvHD in one organ, a further assessment for involvement of other organs is made.

Severity of disease is established using the modified Seattle Glucksberg grading criteria in the case of aGvHD, and as mild/moderate/severe using the National Institutes of Health (NIH) consensus criteria in the case of chronic disease.

A Multi-Disciplinary Team (MDT) is called with the accountable transplant physician, nurse and consultant in whichever organ is principally involved to discuss treatment options available. In the case of aGvHD, the accountable transplant physician is responsible for continuous oversight of treatment. The goal of any treatment is the effective control of GvHD whilst minimising the risk of toxicity and relapse. In many cases, patients are treated

prophylactically where high probability of GvHD is present. Combination therapies are often required.

For patients with aGvHD:

Topical therapies (incl. hydrocortisone, betamethasone, clobetasol and clobetasone)and optimisation of calcineurin inhibitors (tacrolimus or cyclosporine) and/or mycophenolate mofetil are the preferred approaches in the management of grade I disease. Where patients present with grade II-IV GvHD, systemic corticosteroids (methylprednisolone) are indicated first-line. Dosage varies depending on severity, with 1mg/kg/day indicated for patients with grade II and 2mg/kg/day indicated for patients with grades III-IV disease. Where patients present with acute intestinal GvHD and are at risk of developing adverse effects or becoming corticosteroid dependent, non-absorbable steroids (budesonide or beclomethasone) are indicated to reduce dose of systemic steroids. Combination therapy is common in steroid- refractory patients, with the following treatments indicated: mammalian target of rapamycin inhibitors (sirolimus) and/or mycophenolate mofetil. These treatments are off label. Where patients fail to show complete response (i.e. steroid-refractory aGvHD), have developed significant adverse effects to first-line treatments or are steroid- dependent, ECP should be offered.

For patients with cGvHD:

Corticosteroids are indicated as first-line treatments, with an initial starting dose of 1mg/kg prednisolone. Where patients are at risk of developing adverse effects or becoming corticosteroid dependent, concurrent off-label calcineurin inhibitors (tacrolimus or cyclosporine) are indicated to reduce dose of systemic steroids. The use of a calcineurin inhibitor does not represent a line of therapy.

Where patients fail to show complete response (i.e. steroid-refractory cGvHD), have developed significant adverse effects to first-line treatments or are steroid- dependent, sirolimus is indicated. The following treatments are proposed to be added as second-line options (by organ/indication):

1. Refractory cGvHD: Pentostatin (1.5mg/m^2)
2. Skin, oral, liver and pulmonary cGvHD: ECP
3. Refractory cutaneous or musculoskeletal cGvHD: Rituximab
4. Refractory pulmonary or sclerodermatous cGvHD: Imatinib

The use of these drug treatments in cGvHD is off-label. ECP should be the second line treatment of choice for skin, oral, liver and pulmonary cGvHD. However, ECP is not readily available to all transplant centres and patients are often too unwell to travel. For the small proportion for whom ECP may not be suitable, the treatments set out above should be considered. NICE have recommended belumosudil, within its marketing authorisation, for treating cGvHD in people 12 years and over after 2 or more systemic treatments.

Where patients show incomplete response to two different second-line options and/or have developed significant adverse effects, the following treatments are indicated third-line: mycophenolate mofetil, methotrexate and pulsed corticosteroids. These treatments are off-label.

Governance arrangements

Any provider organisation treating patients with this/these intervention/s will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust’s Drugs and

Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Mechanism for funding

Provider organisations must register all patients using prior approval software where a relevant prior approval form exists, for example for belumosudil.

These interventions within the criteria set out in this document will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

Audit requirements

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

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to new evidence, then a Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access to treatment on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

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.

Definitions

Acute Graft versus Host Disease (aGvHD)	A common complication that occurs after an allogenic hematopoietic cell transplant. This occurs when immune cells from the transplanted donor recognise the

	recipient's tissues as foreign and mount an immune response against them. This is referred to as acute, as it usually occurs within 100 days of transplant.
Chronic Graft versus Host Disease (cGvHD)	A complication that occurs after an allogenic haematopoietic cell transplant. This occurs when immune cells from the transplanted donor recognise the recipient's tissues as foreign and mount an immune response against them. This is referred to as chronic, as it usually occurs after 100 days of transplant.
Extracorporeal photopheresis (ECP)	A process of exposing white blood cells to UVA light.
Haematopoietic Stem Cell Transplantation	This was historically referred to as a bone marrow transplant and involves administering healthy hematopoietic stem cells to patients with dysfunctional or depleted bone marrow.

References

References which inform this Clinical Policy are located within evidence summary.