

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

Reference: NHS England: 16069/P



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

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Policy Statement

NHS England will commission treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation 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 graft versus host disease

Graft versus host disease (GvHD) is a frequent complication of bone marrow or stem cell transplantation using tissue from another person. This is called a donor transplant or an allogeneic transplant. 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).

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- 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 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.

About treatments for GvHD

Treatment usually starts with medicines called 'steroids'. Depending on the type of GvHD, the following treatments may be considered by clinicians to treat their patients:

- other medicines that reduce the body's immune response (immunosuppressants)
- a therapy where white blood cells are exposed to UVA light (called 'extracorporeal photopheresis' or ECP)
- an infusion of specially prepared stem cells (called 'mesenchymal' stem cells).

What we have decided

NHS England has carefully reviewed the evidence for treatments for graft versus host disease (GvHD) after stem cell transplantation.

We have concluded that there is enough evidence to consider making the following treatments available:

- patients with acute GvHD - extracorporeal photopheresis (ECP)
- patients with chronic GvHD - ECP, pentostatin, rituximab and imatinib.

However, we have also concluded that there is not enough evidence to make the following treatments available at this time:

- patients with acute GvHD - infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission extracorporeal photopheresis (ECP) for patients with acute graft versus host disease (GvHD) and ECP, pentostatin, rituximab and imatinib for patients with chronic GvHD, and to not routinely commission infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells for patients with acute GvHD, where these patients fall under the remit of specialised commissioning.

GvHD is a complication of allogeneic haematopoietic stem cell transplantation (Allo-HSCT) and can be serious and life threatening. GvHD can affect the skin, mouth, eyes, lung, liver and gut. There are two types of GvHD: acute and chronic. Acute GvHD (aGvHD) generally starts within 100 days of transplant, with chronic GvHD (cGvHD) 100 days after it. Both can present with mild to severe symptoms. First line treatments include topical therapies, systemic corticosteroids or calcineurin inhibitors. Second line or subsequent therapy is guided by grade and clinical presentation of GvHD and treatments of clinical interest include other immunosuppressant therapies such as imatinib and sirolimus, newer biological therapies such as rituximab and infliximab and ECP, and cell therapy such as mesenchymal stem cells. Whilst some treatments are complicated by both severe infection and the risk of relapse of the original malignancy by their effect of dampening the immune system, others have a better profile, e.g. ECP. Clinically, treatment of GvHD is highly individualised, based upon clinical response.

This policy aims to provide clear definitions of each stage of GvHD, and to review the evidence to define the most clinically effective second and third-line non-tariff treatments so that GvHD patients have equal access to appropriate treatments across England. Moreover, this policy applies to all patients who are under the care and commissioning responsibility of NHS England.

2 Definitions

GvHD is a common complication of Allo-HSCT which is a major cause of post-transplant mortality and morbidity. It is caused by immune incompatibility between the graft (donor) and recipient tissues. The graft cells recognise the recipient tissues as foreign, and mount an immune response against them.

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) through II (moderate), III (severe) to 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.

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.

3 Aims and Objectives

This policy aims to define NHS England's commissioning position for non-tariff treatments as part of the treatment pathway for patients of all ages with GvHD.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for patients with GvHD, and equal access to treatment across England.

4 Epidemiology and Needs Assessment

In 2013 there were 1,615 allogeneic transplants (British Society for Blood and Marrow Transplantation).

The BSBMT Outcomes Register (2007-2012) identifies the rate of aGvHD (all grades) for all adult allograft recipients ranges from 31-50% depending on stem cell source (2,180 patients, 2007-2012 cohort). The incidence of the most severe Grade 3-4 categories of aGvHD requiring second or subsequent lines of therapy is below 10% (364 patients, 2007-2012 cohort).

The rate of cGvHD in adult allograft recipients ranges from 30-40% (1,592 patients, 2007-2012 cohort) and is 5-6% for extensive cGvHD (241 patients, 2007-2012 cohort) who will require second or subsequent lines of therapy.

The rate of acute and cGvHD amongst paediatric allograft recipients shows similar incidence compared to adults, and the BSBMT Outcomes Register (2007-2012 cohort) identifies 697 patients with all grades of aGvHD, whilst the incidence of the most severe Grade 3-4 categories is 134 patients.

In the 2007-2012 paediatric patient cohort, 154 patients have cGvHD, while 22 patients have extensive cGvHD.

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of the following treatments for acute and chronic GvHD following HSCT:

Acute: Extracorporeal photopheresis (ECP)

Chronic: ECP, pentostatin, rituximab and imatinib

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 aGvHD following HSCT: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells.

The review process

A joint working group established by the British Committee for Standards in Haematology (BCSH) and BSBMT has reviewed the available literature (as at 2012) concerning the efficacy of available treatments for both acute and chronic GvHD.

A further rapid review of evidence published since then was conducted by the Policy Working Group's Public Health lead to assess any new evidence published since the BSBMT guidelines (2012).

Evidence Summary

ECP

BCSH summary

aGvHD:

ECP is a cell based immune-modulatory therapy. ECP involves processing up to 15% of the patients total blood volume per cycle, isolating a buffy coat (approx 5×10^9 leukocytes) and adding 8-methoxypsoralen followed by UVA irradiation before it is returned to the patient.

There are fewer reports detailing the role of ECP in aGvHD compared to cGvHD. The initial reports included small patient numbers but did suggest efficacy of ECP in the acute setting (Smith et al., 1998; reviewed in Dall'Amico & Messina, 2002). A retrospective series of 23 patients with acute steroid-refractory GvHD reported a complete response rate of 52% although no patients with grade IV GvHD had a complete response (CR).

A trend for improved survival was seen in grade III/IV GvHD compared to matched controls (38% vs 16%; $p=0.08$) (Perfetti et al., 2008). Greinix et al. have published the largest series to date. This phase II prospective study included 59 patients with steroid-refractory or steroid-dependent GvHD treated with 2 consecutive ECP treatments every week. Complete responses were reported in 82% of patients with cutaneous involvement, 61% of liver involvement and 61% with gut involvement (Greinix et al., 2006). At 4 years, transplant-related mortality (TRM) was 36%. The use of ECP in the treatment of aGvHD in the UK has been reported by Das-Gupta et al. In a series of 19 patients with steroid-refractory aGvHD, 11 patients showed a clinical response including 5/10 with grade IV GvHD (Das Gupta et al., 2011).

Positive results have also been reported in children treated with ECP. Perotti et al. report a response rate of 68% in 50 children treated with ECP for aGvHD (2010). The standard UVAR XTS machine is only suitable for children over 40 kg in weight although the newer CELLEX machine is now available which allows treatment of patients <40 kg.

ECP has an acceptable safety profile. The side effects appear to be mild and include hypotension, fevers and reduction of haemoglobin concentration (Greinix et al., 1998, Perotti et al., 1999). There are no reports of increased infection risk or disease relapse. An indwelling catheter is required in patients with poor venous access. At present, access to ECP for aGvHD in the UK is generally limited to those centres where ECP is available on site as patients are often too unwell to travel for treatment. The optimal treatment schedule and duration of treatment has yet to be established. Das Gupta et al. reported a regimen of weekly cycles for a minimum of 8 weeks continued until maximal response or complete response seen (Das Gupta et al., 2011).

cGvHD:

ECP has been widely used as a second line therapy for the treatment of mucocutaneous cGvHD, with consistently high complete response rates of up to 80% with cutaneous manifestations, and significant improvement in sclerodermatous skin involvement (Couriel et al., 2006b; Dignan et al., 2011).

Flowers et al. (2008) published the first multicentre, randomised controlled, prospective Phase II trial of ECP in the treatment of patients with cGHVD. This study included patients who were steroid dependent, steroid refractory and those who were intolerant of steroids. Ninety-five patients were randomised to receive either ECP and standard therapy (corticosteroids plus other immunosuppressive agents including ciclosporin, tacrolimus or mycophenolate mofetil) or standard therapy alone. The study used percentage improvement in total skin scores after 12 weeks of ECP treatment as the primary endpoint. The percentage reduction in total skin score from baseline was greater in the ECP arm compared to the non-ECP arm but this did not achieve statistical significance ($p=0.48$). The proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease in total skin score was 8.3% in the ECP arm at week 12 and 0% in the control arm ($p=0.04$) (Flowers et al., 2008). A major limitation of this study is that the study arm assignment was known to physicians who were controlling the prednisolone dose. This study has several other limitations due to the methodological challenges of conducting clinical trials in patients with cGvHD. These include the short duration of treatment, only using skin

as the primary endpoint to assess response, the limited time allowed for reduction in steroids (6 weeks) and the large variation in immunosuppressive regimens used.

The response reported in patients with visceral GvHD, e.g. liver, is more variable. Greinix et al. (2006) reported a complete response rate of 68% for liver cGvHD (17/25 patients). Similarly, Couriel et al. (2006b) reported a partial response rate of 15/21 (71%) for liver cGvHD. These results have not been reflected in all studies (Seaton et al., 2003; Foss et al., 2005). Lung and gut involvement have demonstrated less consistent responses (Greinix et al., 1998; Child et al., 1999, Couriel et al., 2006b). There are mixed reports of the benefits of earlier (<12 months) versus delayed treatment with ECP (Child et al., 1999; Apisarnthanarax et al., 2003; Messina et al., 2003; Foss et al., 2005). Response to ECP has been associated with increased survival and reduction in the use of corticosteroids (Foss et al., 2005).

Additional evidence review (post 2012 papers)

aGvHD and cGvHD:

Note: systematic review of prospective studies study may include papers already reviewed by BCSH

The review found five additional studies of ECP which met the inclusion criteria: one Cochrane systematic review of randomised controlled trials, one systematic review of prospective studies, one prospective cohort study, and two retrospective case series.

The Cochrane review included randomised controlled trials of ECP with or without alternative treatment versus alternative treatment alone in paediatric patients with cGvHD after haematopoietic stem cell transplantation. No studies were found which met the inclusion criteria.

The systematic review of prospective studies included nine prospective cohort studies of second-line ECP for steroid refractory or steroid dependent acute and/or cGvHD, together including a total of 323 subjects. The review excluded studies with less than five subjects. A random effects model was used in the meta-analysis. An overall clinical response was found of 69% (95% CI 34-95%) in aGvHD and 64%

(95% CI 47-79%) in cGvHD. Organ specific-response rates were also reported, for aCvHD and cGvHD separately. The highest response rates were seen for GvHD affecting the skin and gastrointestinal tract. Rates of immunosuppression discontinuation were 55% (95% CI, 40% to 70%) and 23% (95% CI, 7% to 44%) for acute and cGVHD, respectively. This was a well-conducted systematic review, but was limited by the small number and size of prospective studies included, and considerable heterogeneity was found.

The prospective cohort study was an international study involving three centres, and including a total of 128 patients with steroid-refractory or steroid-dependent aGvHD. The primary outcome was 6-month freedom from treatment failure, as defined by the absence of death, relapse/progression of malignancy, or a further line of systemic immunosuppressive therapy within 6 months of intervention. The incidence of 6-month freedom from treatment failure was 77.3% with a 2-year overall survival of 56%. Higher grade of aGvHD (grade 2 versus grades 3-4) at onset of ECP predicted for poor outcome as measured by survival, non-relapse mortality and 6-month freedom from treatment. This was a relatively large and well-conducted study.

The two retrospective case series were both small studies, one of ECP for aGvHD, and the other of ECP for both acute and cGvHD, of nine and 21 subjects respectively. The primary outcome in both studies was clinical response rate, and the secondary outcome was reduction in steroid dose. In the first study all nine patients responded and the average dose of steroid was reduced, but all patients subsequently developed cGvHD. In the second of these studies nine out of the 13 subjects with cGvHD responded to ECP, and three out of the nine with aGvHD. Steroid was stopped or dose reduced in all of the cGvHD subjects, but was unchanged in the aGvHD group. This study also reported a 4-year overall survival of 67.7 in the cGvHD group. There were no 4-year survivors in the aGvHD group.

We found no studies of cost-effectiveness, and no formal studies of safety, although adverse effects were reported in the studies above. These include gastro-intestinal bleeding, renal failure/sepsis, urosepsis, acute respiratory distress syndrome, pneumothorax, pneumonia, pleural effusion, ischaemic heart disease,

cytomegalovirus colitis, and line-related complications. It is very unclear how many of these complications were directly attributable to ECP.

aGvHD – other proposed indications

Infliximab

BCSH summary

Several studies have investigated the role of blocking the inflammatory cytokine TNF α . TNF α is involved in the pathophysiology of GvHD by activating antigen presenting cells, recruiting effector cells and causing direct tissue damage (Reddy et al., 2003). Earlier animal models had suggested that TNF played a major role in aGvHD of gastrointestinal tract and skin (Hattori et al., 1998). Reports have investigated both the role of infliximab and etanercept.

Infliximab is an anti-TNF α monoclonal antibody. Several small case series suggested a possible benefit of infliximab in the treatment of steroid-refractory GvHD (Patriarca et al., 2004; Couriel et al., 2004; Kobbe et al., 2001; Hervé et al., 1992). There are also reports of an increased risk of infection in patients treated with infliximab (Marty et al., 2003). In a larger study of 52 patients (71% of whom had grade III/IV GvHD), 15% achieved a complete response with infliximab as salvage therapy (Pidala et al., 2009). In addition, a phase 3 study of 63 patients comparing infliximab plus corticosteroids to corticosteroids alone in aGvHD did not show any improvement in response rate or overall survival in patients with newly diagnosed aGvHD (Couriel et al., 2009).

Additional evidence review (post 2012 papers)

The review found one retrospective case series of infliximab in 10 paediatric patients with severe steroid refractory aGVHD of the gastrointestinal tract. All patients received 10 mg/kg infliximab weekly for 3–4 doses. Eight patients had a complete clinical response and two had partial response.

All patients developed infections subsequently. Five patients developed cGVHD. Six patients died at 66–1451 days post-transplant, (from infection, aGVHD, lung cGVHD,

or pneumonia. Four patients were alive at 238–924 days. This study represented poor quality evidence.

Etanercept

BCSH summary

Etanercept is a soluble dimeric TNF α receptor 2 which renders TNF α inactive by competing for binding sites (Sieper et al., 2005). The drug is administered subcutaneously and has a good side effect profile (Sieper et al., 2005). Etanercept has been used in several studies in the primary treatment of aGvHD. A pilot study reported a 75% response rate in 20 patients with grade II/III aGvHD treated with etanercept and methylprednisolone (Uberti et al., 2005).

A further phase II study was reported by the same group comparing etanercept plus methylprednisolone in 61 patients (20 of whom had been included in the pilot study) compared to a contemporaneous group of 99 patients who received steroids alone for initial treatment of aGvHD. Patients treated with etanercept were more likely to achieve a complete response than those treated with steroids alone (69% vs 33%, $p < 0.001$) (Levine et al., 2008). Busca et al. reported a response in 6/13 patients with refractory gut GvHD (2007). Both of these studies suggested that the GI tract was particularly sensitive to TNF blockade. The infection rate was not significantly different between the two populations. Two-thirds of the patients had grade II disease.

Additional evidence review (post 2012 papers)

The review found one retrospective case series of etanercept for steroid refractory aGvHD in 18 patients. All received 25mg of etanercept subcutaneously twice weekly for 4 weeks. Using nonparametric tests, etanercept had a down-grading effect on aGvHD ($p=0.005$), although no patients achieved a complete remission. 50% had a partial response, with significant improvements in skin and gut GvHD. There was no significant effect on hepatic GvHD. Four patients died of fatal infections.

Inolimomab

BCSH summary

The interleukin-2 receptor alpha subunit (CD25) is predominantly expressed on activated T lymphocytes and has been a particular target for monoclonal antibody treatment for GvHD.

Inolimomab is a murine anti-IL-2R. Bay et al. retrospectively evaluated the use of inolimomab in 85 patients with steroid-refractory aGvHD (2005). The total response rate was 63% and overall survival at a median follow-up of 20 months was 26%. A further retrospective study of 40 patients reported a 58% response rate with higher responses in those without gastrointestinal disease (Pinana et al., 2006).

Additional evidence review (post 2012 papers)

No additional papers found.

Alemtuzumab

BCSH summary

Alemtuzumab (Campath 1H) is a humanised, unconjugated IgG1 kappa monoclonal antibody that is specific for CD52 receptors present on mature T and B lymphocytes, monocytes, monocyte-derived dendritic cells, macrophages and eosinophils (Hale, 2001).

Several case reports suggested that alemtuzumab may be helpful in the management of aGvHD (Varadi et al., 1996; Carella et al., 2004; Wandroo et al., 2004). In a prospective study, 18 patients with steroid-refractory aGvHD received alemtuzumab 10mg subcutaneously once daily for five days. At day 28, 83% had responded to alemtuzumab and 10/15 of responders were alive after a median follow up of 11 months. Infectious complications were reported in 14 patients including CMV reactivation in 11 patients (Gomez-Almaguer et al., 2008). In a series of 20 patients with histologically confirmed grade III/IV steroid refractory GvHD, the overall response rate was 70% and one year overall survival was 50% (Schnitzler et al., 2009). These results have not been replicated in all studies. In a phase II trial of 10 patients, five patients responded but all died within a median of 40 days of treatment

(Martinez et al., 2009). These studies were predominantly undertaken in patients who had not received T cell depletion prior to transplantation and it is possible that the effect may be different in T cell depleted patients.

Additional evidence review (post 2012 papers)

The review found two small retrospective case series of alemtuzumab for aGvHD.

One retrospective study included 24 patients with grades II, III or IV steroid refractory aGvHD treated with varying doses of alemtuzumab. A response to treatment was reported in 15 patients (62.4%). A complete response was seen in 11 patients (45.8%), and a partial response in 4 patients (16.6%). The overall survival rate at 1 year for all patients was 33.3% (95% CI 15.9% to 51.9%) and for responders, 53.3% (95% CI, 26.3% to 74.4%). Two patients died from infection, five patients from recurrent GVHD, and one from an uncontrolled post-transplant lymphoproliferative disorder.

The other study included 19 paediatric patients, also with steroid refractory grades II, III and IV aGvHD, who received a median dose of 0.9mg/kg alemtuzumab (range 0.3–2 mg/kg) divided over 2–6 days. 89% of patients received additional courses. A complete response, defined as GVHD of grade 0 at four weeks following the first alemtuzumab course, was observed in nine patients (47%). A partial response, defined as an improvement in grade after four weeks, was observed in five patients (26%). There was no response in five patients (26%). The overall response rate at four weeks was 73%. Infectious complications included bacteraemia (47%), presumed or documented fungal infections (21%), adenovirus viremia (52%), Epstein-Barr virus (EBV) viremia (36%), and Cytomegalovirus (CMV) viremia (36%).

Pentostatin

BCSH summary

Pentostatin is a nucleoside analogue which is a potent inhibitor of adenosine deaminase. Cell death occurs as a result of accumulation of 2-deoxyadenosine 5-triphosphate, particularly in T cells and NK cells. The drug also causes reduced

TNF α and prolonged lymphopenia (Margolis et al., 2000; Foss, 2006). It has been used in the treatment of both aGvHD and cGvHD.

A phase I study of 23 evaluable patients found the maximum tolerated dose to be 1.5mg/m² per day for 3 days. 14 patients achieved a complete response but median survival was 85 days (Bolanos-Meade et al., 2005). A small retrospective series including 12 patients with aGvHD reported overall response in 6/12 patients but median survival of only 1.4 months (Pidala et al., 2010). Pentostatin was also used in combination with corticosteroids in one arm of a randomised phase II study for initial therapy of aGvHD comparing etanercept, mycophenolate mofetil and denileukin. The day 28 complete response rate was 38% which was lower than mycophenolate mofetil (MMF) (60%) and denileukin (53%). Overall survival at 9 months was 47% which was similar to denileukin and etanercept but lower than MMF (64%). The infection rate of 57% was also higher compared to MMF (44%) and etanercept (48%) (Alousi et al., 2009). A recent study including 23 patients with steroid-refractory aGvHD reported an 83% response rate with a 2 year survival rate of 43% (Klein et al., 2011).

Additional evidence review (post 2012 papers)

No additional papers found.

Mesenchymal stem cells

BCSH summary

Mesenchymal (stromal) stem cells (MSCs) are a population of undifferentiated pluripotent stem cells that modulate immune and inflammatory response and facilitate repair of connective tissues (Pittenger et al., 1999; Majumdar et al., 2000). Le Blanc et al. were the first to report efficacy of MSCs for the treatment of aGvHD (2004). A phase II study of MSCs in patients with refractory GvHD was subsequently undertaken by the same group. This report included 55 patients (25 children, 30 adults) with steroid-resistant, severe aGvHD. Thirty patients had a complete response and 9 showed improvement. Overall survival at 2 years post-transplant was 53% in complete responders, compared to 16% in those who did not respond (Le Blanc et al., 2008). There were no significant adverse events. A report by Karlsson et

al. suggests that MSCs have little effect on T cell responses to EBV and CMV, despite their strong immunosuppressive effects on alloreactive T cells (Karlsson et al., 2008).

Prochymal MSCs have been used as part of a compassionate use programme. In 12 children with grade III or IV gut GvHD a complete response was seen in 7 patients and 5/12 were alive after a median follow-up of 611 days (Prasad et al., 2011). The same commercially generated MSCs have recently been used in a multicentre randomised controlled trial which has been reported in abstract form. 163 patients received MSCs and 81 received placebo. Although this study did not show improved complete response rates overall in steroid-refractory aGvHD compared to the control arm, patients with steroid-refractory gut and liver aGvHD showed significantly improved response rates (82% and 76% respectively) (Martin et al., 2010). Furthermore, it should be noted that not all sources of MSCs are equivalent.

A recent report used MSCs for the primary treatment of aGvHD in combination with corticosteroids. Thirty-one evaluable patients were included and were randomised to receive a dose of either 2 or 8 million MSCs/kg. Seventy-seven percent of patients had a complete response rate and 16% had a partial response rate. There were no differences in safety or efficacy between the two groups (Kebriaei et al., 2009). Some success has also been reported using MSCs expanded in vitro with human serum (Perez-Simon et al., 2011). This study includes 10 adult patients with acute refractory GvHD and demonstrated a complete response in one patient, a partial response in 6 patients and no response in the remaining 3 patients.

MSCs are currently available in the UK for paediatric patients with steroid refractory aGvHD as part of the Prochymal compassionate use programme from Genzyme. In addition, for both adults and children MSCs may be available from Imperial College. A randomised study using MSC in upfront therapy of grade III-IV aGvHD is also planned. MSCs are a promising treatment in the management of aGvHD. At present the authors suggest that MSCs may have a role in third line treatment options but recognise that this is an area of active research and that MSCs may have a greater role in the management of aGvHD in the future.

Additional evidence review (post 2012 papers)

No additional papers found.

cGvHD – other proposed indications

Pentostatin

BCSH summary

A Phase II study administered pentostatin fortnightly for 12 doses and reported a response rate of 55% in 58 heavily pre-treated patients with refractory cGvHD (Jacobsohn et al., 2007). A clearly defined scoring system was used to assess patients at 3-monthly intervals and 31 patients were considered to have a major response according to the study criteria. Survival was 70% at 2 years and 11 infectious episodes were possibly related to pentostatin. The same investigators reported a 53% response rate in a Phase II study of 51 children with refractory cGvHD (Jacobsohn et al., 2009). Similarly, a clearly defined scoring system was used to assess response at 3-monthly intervals and seven patients had a complete response and 20 had a partial response. Overall survival at one year was 84%. There were 27 episodes of infection occurring in 15 patients. A dose of 4 mg/m² was administered intravenously every 2 weeks in these reports and the main toxicities were infection and haematotoxicity. In a retrospective series, 10/18 patients with refractory cGvHD obtained a complete or partial response to pentostatin treatment (Pidala et al., 2010). As infections are frequent, it has been recommended that pentostatin is not used in the context of acute infection or in pulmonary cGvHD (Wolff et al., 2011).

Additional evidence review (post 2012 papers)

No additional papers found.

Rituximab

BCSH summary

Rituximab is an anti-CD20 monoclonal antibody used widely in the management of B-cell malignancies. Ratanatharathorn et al. (2000) reported the first case of a patient

with cGvHD and immune thrombocytopenia having a complete response to four doses of 375 mg/m² of rituximab. Cutler et al. (2006) reported the results of a Phase I/II study that included 21 patients with steroid-refractory cGvHD treated with 375 mg/m² weekly of rituximab. A response rate of 70% was observed although many responses were partial and limited to cutaneous and musculoskeletal disease. In addition, many patients had relatively mild GvHD. Responses were durable for one year (Cutler et al., 2006). A further Phase II study of 37 patients reported 8 complete and 24 partial responses with higher responses in skin, oral cavity and musculoskeletal systems (Kim et al., 2010). Similar results have been reported in retrospective series (Zaja et al., 2007; Mohty et al., 2008). A small retrospective study of 13 patients reported a similar response rate of 69% using a dose of 50 mg/m² weekly for 4 weeks (von Bonin et al., 2008). A recent meta-analysis reviewed seven studies with a total of 111 patients (Kharfan-Dabaja et al., 2009). The pooled response rate was 66% and common adverse events were infusion reactions or infectious complications (Kharfan-Dabaja et al., 2009).

Additional evidence review (post 2012 papers)

Note: systematic review of prospective studies may include papers already reviewed by BCSH

The review found one systematic review of prospective and retrospective studies of rituximab for cGvHD. All prospective studies evaluating the efficacy of rituximab in GVHD were included in this review, regardless of the number of patients enrolled. Retrospective studies were included if they evaluated the efficacy of rituximab in cGVHD in a minimum of five patients.

Single case reports were excluded. Seven studies (3 prospective and 4 retrospective, with a total of 111 patients) met the inclusion criteria. Data were pooled under a random-effects model. The pooled proportion of overall clinical response was 0.66 (95% confidence interval 0.57 to 0.74). There was no statistical heterogeneity among the pooled studies. Response rates were 13% to 100% for cGVHD of the skin, 0 to 83% for cGVHD of the oral mucosa, 0 to 66% for cGVHD of the liver, and 0 to 38% for cGVHD of the lung. Common adverse events were related to infusion reactions or infectious complications.

The studies included in this review were all small, non-controlled studies with sample sizes ranging from 3 to 28 patients. The pooled response rates mask variation between individual studies. The heterogeneity of the patients enrolled, different criteria for assessing response rates, range of diseases and previous interventions undermine the quality of the results and ability to determine the true effect of rituximab.

Imatinib

BCSH summary

Imatinib is a tyrosine kinase inhibitor used in the management of chronic myeloid leukaemia (CML) and stromal gastrointestinal tumours (Giralt et al., 2007; Blanke, 2010). It is likely that it exerts its effect by dual inhibition of transforming growth factor b (TGF-b) and platelet-derived growth factor (PDGF) pathways. Blockade of these pathways has been shown to reduce fibrosis in experimental models thereby making imatinib a possible candidate for the management of fibrotic diseases including cGvHD (Bonner, 2004; Ghofrani et al., 2005).

Majhail et al. (2006) reported a patient with relapsed CML and bronchiolitis obliterans who obtained a molecular remission with imatinib and an improvement in their respiratory symptoms. A retrospective study reported a 50% response rate (two complete responses, five partial responses) in 14 patients with refractory sclerotic GvHD (Magro et al., 2009). Response was assessed using a recognised skin score and a partial response was defined as a >50% improvement in skin score. Olivieri et al. (2009) reported a 79% response rate (seven complete responses, eight partial responses) at 6 months in a prospective pilot study of 19 patients with refractory disease. Complete or partial responses were observed in 7/11 patients with mild pulmonary cGvHD (Olivieri et al., 2009). Partial response was defined as an improvement in pulmonary function test or 50% reduction in corticosteroid dose. Overall survival at 18 months was 85%. A small pilot study suggested that imatinib shows best responses in those with mild pulmonary cGvHD and is not effective in severe disease (Stadler et al., 2009). Side effects included dyspnoea, fluid retention

and haematological toxicity. The initial dose used was 100–200 mg, which was subsequently titrated to 400 mg if well tolerated.

Additional evidence review (post 2012 papers)

No additional papers found.

6 Criteria for Commissioning

aGvHD

NHS England will routinely commission ECP in accordance with the patient pathway (see section 9) for patients meeting the following criteria

Inclusion criteria:

(i) 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

(ii) Is unsuitable for, 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:

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

Stopping criteria:

(i) Patients who do not have a positive response, develop severe toxicity, or for whom the treatment has no effect.

cGvHD

NHS England will routinely commission ECP, pentostatin, rituximab and imatinib in accordance with the patient pathway (see section 9) for patients meeting the following criteria

Inclusion criteria:

(i) 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

(ii) Is unsuitable for, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of systemic corticosteroids, calcineurin inhibitors and/or sirolimus).

Exclusion criteria:

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

Stopping criteria:

(i) Patients who do not have a positive response, develop severe toxicity, or for whom the treatment has no effect.

7 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 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, eumovate, betnovate and dermovate) 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.

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, calcineurin inhibitors (tacrolimus or cyclosporine) are indicated to reduce dose of systemic steroids.

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/m²)
2. Skin, oral, liver and pulmonary cGvHD: ECP
3. Refractory cutaneous or musculoskeletal cGvHD: Rituximab
4. Refractory pulmonary or sclerodermatous cGvHD: Imatinib

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 sick to travel. For the small proportion for whom ECP may not be suitable, the other treatments set out above should be considered.

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.

8 Governance Arrangements

All providers of HSCT must be Joint Accreditation Committee-ISCT & EBMT (JACIE) accredited. NHS England will commission from specialised HSCT centres, who will provide oversight of diagnosis of GvHD and initiation of ECP. Following a further process to identify providers of ECP, there will be scope to put in place shared care arrangements subject to local governance and JACIE international standards accreditation.

The governance arrangements are described in detail in the BMT service specifications for adults (B04/S/a) and children (B04/S/b) respectively.

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9 Mechanism for Funding

The funding arrangements are described in detail in the service specifications. At present, responsibility for funding GvHD sits with NHS England for the first 100 days post-transplant. After this, it transfers to CCGs. This policy applies to all patients who are the responsibility of NHS England specialised commissioning.

10 Audit Requirements

Complete data must be submitted to the BSBMT 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 undergo regular JACIE inspection. All centres must also provide the data required for the BMT Quality Dashboard.

Audit requirements are described in more detail in the BMT service specification.

11 Documents which have informed this Policy

The British Society of Haematology Guidelines for the treatment of GvHD, 2012

12 Date of Review

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

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