GvHD
Summary of available evidence

ECP

Acute and chronic GvHD

ECP
Acute and chronic GvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
2nd line treatment	**Extracorporeal photopheresis** (Procedure)	Steroid refractory aGvHD	**British Committee for Standards in Haematology (BCSH) summary for acute GvHD** Extracorporeal photopheresis (ECP) is a cell based immune-modulatory therapy which offers a different therapeutic approach. ECP involves processing up to 15% of the patients total blood volume per cycle, isolating a buffy coat (approx 5 x 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 chronic GvHD. 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[1]). 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[2]). Greinix *et al* have published the largest series to date. This phase 2 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[3]). At 4 years, 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[4]). 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 (Perotti *et al*, 2010[5]). 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 excellent safety profile. The side effects appear to be mild and include hypotension, fevers and reduction of haemoglobin concentration (Greinix *et al*, 1998[6], Perotti *et al*, 1999[7]). 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). *Summary continues on next slide*	Routinely commissioned

ECP
Acute and chronic GvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
2nd line treatment	**Extracorporeal photopheresis** (Procedure) *Cont'd*	Skin, oral, liver cGvHD	**BCSH summary for chronic GvHD** Extracorporeal photopheresis (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[8]; Dignan et al, 2011[9]). Flowers et al (2008) published the first multicentre, randomized 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 randomized 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[10]). 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[11]; Foss et al, 2005[12]). Lung and gut involvement have demonstrated less consistent responses (Greinix et al, 1998; Child et al, 1999[13]; 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[14]; Messina et al, 2003[15]; Foss et al, 2005). Response to ECP has been associated with increased survival and reduction in the use of corticosteroids (Foss et al, 2005). *Summary continues on next slide*	Routinely commissioned

ECP
Acute and chronic GvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
2nd line treatment	**Extracorporeal photopheresis** (Procedure)	Steroid refractory aGvHD AND Skin, oral, liver cGvHD	**Additional evidence review (post-2012 papers), acute and chronic GvHD** *Note: systematic review of prospective studies study may incl. papers already reviewed by BCSH* We found 5 additional studies of ECP which met our 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[16] included randomised controlled trials of ECP with or without alternative treatment versus alternative treatment alone in paediatric patients with chronic GvHD after haematopoietic stem cell transplantation. No studies were found which met the inclusion criteria. The systematic review of prospective studies[17] included 9 prospective cohort studies of second-line ECP for steroid refractory or steroid dependent acute and/or chronic GvHD, together including a total of 323 subjects. The review excluded studies with less than 5 subjects. A random effects model was used in the meta-analysis. An overall clinical response was found of 69% (95% confidence interval 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 chronic GVHD, 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[18] was an international study involving 3 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[19, 20] were both small studies, one of ECP for aGvHD, and the other of ECP for both acute and chronic GvHD, of 9 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 9 patients responded and the average dose of steroid was reduced, but all patients subsequently developed cGvHD. In the second of these studies 9 out of the 13 subjects with cGvHD responded to ECP, and 3 out of the 9 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.	Routinely commissioned

Acute GvHD

Acute GvHD
aGvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
Addition of 2nd line agents considered in patients who have failed to respond to methylprednisolone (2mg/kg) in conjunction with calcineurin inhibitors				
2nd line treatment	Anti-TNF: **Infliximab**	Steroid refractory GvHD	**BCSH summary** Several studies have investigated the role of blocking the inflammatory cytokine TNFα. TNFα is involved in the pathophysiology of GvHD by activating antigen presenting cells, recruiting effector cells and causing direct tissue damage (Reddy *et al*, 2003[21]). Earlier animal models had suggested that TNF played a major role in aGvHD of gastrointestinal tract and skin (Hattori *et al*, 1998[22]). Reports have investigated both the role of infliximab and etanercept. Infliximab is an anti-TNFα monoclonal antibody. Several small case series suggested a possible benefit of infliximab in the treatment of steroid-refractory GvHD (Patriarca *et al*, 2004[23]; Couriel *et al*, 2004[24]; Kobbe *et al*, 2001[25]; Hervé *et al*, 1992[26]) There are also reports of an increased risk of infection in patients treated with infliximab (Marty *et al*, 2003[27]). 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[28]). 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[29]). **Additional evidence review (post-2012 papers)** We found one retrospective case series[30] 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 chronic GVHD (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 represents very poor quality evidence.	Not routinely commissioned
	Anti-TNF: **Etanercept**		**BCSH summary** Etanercept is a soluble dimeric TNFα receptor 2 which renders TNFα inactive by competing for binding sites (Sieper *et al*, 2005[31]). 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[32]). 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[33]). Busca *et al* reported a response in 6/13 patients with refractory gut GvHD (Busca *et al*, 2007[34]). 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. *Summary continues on next slide*	Not routinely commissioned

Acute GvHD

aGvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
Addition of 2nd line agents considered in patients who have failed to respond to methylprednisolone (2mg/kg) in conjunction with calcineurin inhibitors				
2nd line treatment	**Etanercept** *Cont'd*	Steroid refractory GvHD	**Additional evidence review (post-2012 papers)** We found one retrospective case series[35] of etanercept for seroid refractory aGvHD in 18 patients. All received 25 mg of etanercept subcutaneously twice weekly for 4 weeks. Using nonparametric tests, etanercept had a down-grading effect on acute GVHD (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.	*Cont'd* Not routinely commissioned
2nd line treatment	Interleukin 2 receptor antibodies: **Inolimomab**	Steroid refractory GvHD	**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 (Bay *et al*, 2005[36]). 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[37]). **Additional evidence review – N/A (proposed as Not routinely commissioned)**	Not routinely commissioned
3rd line treatments are reserved for patients with acute steroid-refractory disease, who have failed at least two different second line treatment options				
3rd line treatment	**Alemtuzumab** (10mg/day)	Acute steroid refractory GvHD	**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[38]). Several case reports suggested that alemtuzumab may be helpful in the management of aGvHD (Varadi *et al*, 1996[39]; Carella *et al*, 2004[40]; Wandroo *et al*, 2004[41]). In a prospective study, 18 patients with steroid-refractory aGvHD received alemtuzumab 10mg subcutaneously once daily for 5 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[42]). 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[43]). These results have not been replicated in all studies. In a phase 2 trial of 10 patients, 5 patients responded but all died within a median of 40 days of treatment (Martinez *et al*, 2009[44]). 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. *Summary continues on next slide*	Not routinely commissioned

Acute GvHD
aGvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
3rd line treatments are reserved for patients with acute steroid-refractory disease, who have failed at least two different second line treatment options				
3rd line treatment	**Alemtuzumab** *Cont'd*	Acute steroid refractory GvHD	**Additional evidence review (post-2012 papers)** We found two small retrospective case series of alemtuzumab for acute GvHD. One retrospective study[45] 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% confidence interval [CI], 15.9% to 51.9%) and for responders, 53.3% (95% CI, 26.3% to74.4%). Two patients died from infection, 5 patients from recurrent GVHD, and 1 from an uncontrolled post-transplant lymphoproliferative disorder. The other study[46] included 19 paediatric patients, also with steroid refractory grades II, III and IV aGvHD, who received a median dose of 0.9 mg/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 bacteremia (47%), presumed or documented fungal infections (21%), adenovirus viremia (52%), EBV viremia (36%), and CMV viremia (36%).	*Cont'd* Not routinely commissioned
	Pentostatin (1.5mg/m2)		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 TNFα and prolonged lymphopenia (Margolis *et al*, 2000[47]; Foss, 2006[48]). It has been used in the treatment of both aGvHD and chronic GvHD. A phase 1 study of 23 evaluable patients found the maximum tolerated dose to be 1.5 mg/m2 per day for 3 days. 14 patients achieved a complete response but median survival was 85 days (Bolanos-Meade *et al*, 2005[49]). 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[50]). Pentostatin was also used in combination with corticosteroids in one arm of a randomised phase 2 study for initial therapy of acute graft-versus-host disease comparing etanercept, mycophenolate mofetil and denileukin. The day 28 complete response rate was 38% which was lower than 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[51]). 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[52]). **Additional evidence review – N/A (proposed as Not routinely commissioned)**	Not routinely commissioned

Acute GvHD

aGvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
3rd line treatments are reserved for patients with acute steroid-refractory disease, who have failed at least two different second line treatment options				
3rd line treatment	**Mesenchymal stem cells** *Cont'd*	Acute steroid refractory GvHD	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[53]; Majumdar *et al*, 2000[54]). Le Blanc *et al* were the first to report efficacy of MSCs for the treatment of aGvHD (LeBlanc *et al*, 2004[55]). A phase 2 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[56]). There were no significant adverse events. An encouraging 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[57]) 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[58]). 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[59]). 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[60]). Some success has also been reported using MSCs expanded in vitro with human serum (Perez-Simon *et al*, 2011[61]). 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 (Professor Francesco Dazzi). A randomised study using MSC in upfront therapy of grade 3-4 aGvHD is also planned. MSCs are a promising treatment in the management of acute GvHD. At present the authors suggest that MSCs may be considered as a third line treatment option 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 – N/A (proposed as Not routinely commissioned)**	Not routinely commissioned

Chronic GvHD

Chronic GvHD

cGvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
2nd line treatments are used in the management of steroid-refractory cGvHD or in patients who are steroid-dependent or intolerant of steroids. Some agents may be used sequentially or in combination, depending on clinical judgement				
2nd line treatment	**Pentostatin**	Refractory cGvHD	A Phase 2 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[62]). 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 2 study of 51 children with refractory cGvHD (Jacobsohn et al, 2009[63]). 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[50]). 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[64]). **Additional evidence review did not find any additional published research**	Routinely commissioned
	Rituximab	Refractory cutaneous or musculoskeletal cGvHD)	Rituximab is an anti-CD20 monoclonal antibody used widely in the management of B-cell malignancies. Ratanatharathorn et al (2000)[65] reported the first case of 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 1/2 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[66]). A further Phase 2 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[67]). Similar results have been reported in retrospective series (Zaja et al, 2007[68]; Mohty et al, 2008[69]). 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[70]). A recent meta-analysis reviewed seven studies with a total of 111 patients (Kharfan- Dabaja et al, 2009[71]). 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 retrospective studies may incl. papers already reviewed by BCSH* We found one systematic review[71] of prospective and retrospective studies of rituximab for chronic GvHD. 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 5 patients. *Summary continues on next slide*	Routinely commissioned

Chronic GvHD

cGvHD

Line	Intervention	Indication	Evidence summary	Proposed commissioning position
2nd line treatments are used in the management of steroid-refractory cGvHD or in patients who are steroid-dependent or intolerant of steroids. Some agents may be used sequentially or in combination, depending on clinical judgement				
2nd line treatment	**Rituximab *Cont'd***	Refractory cutaneous or musculoskeletal cGvHD)	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. Heterogeneity in patients enrolled, different criteria for assessing response rates, range of diseases and previous interventions undermine quality of results and ability to determine true effect of rituximab.	*Cont'd* Routinely commissioned
	Imatinib	Refractory pulmonary or scleroderma tous cGvHD	Imatinib is a tyrosine kinase inhibitor used in the management of chronic myeloid leukaemia (CML) and stromal gastrointestinal tumours (Giralt et al, 2007[72]; Blanke, 2010[73]). 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[74]; Ghofrani et al, 2005[75]). Majhail et al (2006)[76] 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[77]). Response was assessed using a recognized 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[78]). 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[79]). 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 did not find any additional published research**	Routinely commissioned

References

References (1/5)

(1) Dall'Amico, R.& Messina, C. (2002) Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. *Therapeutic Apheresis,* **6**, 296-304.

(2) Perfetti, P., Carlier, P., Strada, P., Gualandi, F., Occhini, D., Van Lint, M.T., Ibatici, A., Lamparelli, T., Bruno, B., Raiola, A.M., Dominietto, A., Di Grazia, C., Bregante, S., Zia, S., Ferrari, G.M., Stura, P., Pogliani, E. & Bacigalupo, A. (2008) Extracorporeal photopheresis for the treatment of steroid refractory aGvHD. *Bone Marrow Transplantation,* **42**, 609-17.

(3) Greinix, H.T., Knobler, R.M., Worel, N., Schneider, B., Schneeberger, A., Hoecker, P., Mitterbauer, M., Rabitsch, W., Schulenburg, A.& Kalhs, P. (2006) The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica,* **91**, 405-8.

(4) Das-Gupta, E., Watson, J. Byrne, J.& Russell, N. (2011) A single centre experience of the efficacy of extracorporeal photopheresis in the treatment of steroid-refractory acute graft-versus-host disease. *Bone Marrow Transplantation,* **46,** S114.

(5) Perotti C, Del Fante C, Tinelli C, Viarengo G, Scudeller L, Zecca M, Locatelli F, Salvaneschi L. (2010) Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. *Transfusion,* **50**,1359-69.

(6) Greinix, H.T., Volc-Platzer, B., Rabitsch ,W. Gmeinhart, B., Guevara-Pineda, C., Kalhs, P., Krutmann, J., Hönigsmann,H., Ciovica, M. & Knobler, R.M. (1998) Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood*, **92**:3098–104.

(7) Perotti, C., Torretta ,L., Viarengo, G. Roveda, L., Bernuzzi, S., Carbone, S., Del Fante, C., La Torre, R., Locatelli, F., Bonetti, F., Gabba, P., Bellosta, M. & Salvaneschi, L.(1999) Feasibility and safety of a new technique of extracorporeal photochemotherapy: experience of 240 procedures. *Haematologica*, **84**:237–41.

(8) Couriel, D.R., Hosing, C., Saliba, R., Shpall, E.J., Anderlini, P., Rhodes, B., Smith, V., Khouri, I., Giralt, S., de Lima, M., Hsu, Y., Ghosh, S., Neumann, J., Andersson, B., Qazilbash, M., Hymes, S., Kim, S., Champlin, R. & Donato, M. (2006b) Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. *Blood*, 107, 3074–3080.

(9) Dignan, F.L., Greenblatt, D., Cox, M., Cavenagh, J., Oakervee, H., Apperley, J.F., Fielding, A.K., Pagliuca, A., Mufti, G., Raj, K., Marks, D.I., Amrolia, P., Peniket, A., Medd, P., Potter, M.N., Shaw, B.E. & Scarisbrick, J.J. (2011) Efficacy of bimonthly extracorporeal photopheresis in refractory chronic mucocutaneous GVHD. *Bone Marrow Transplantation*, 19. doi: 10.1038/ bmt.2011.186 [Epub ahead of print].

(10) Flowers, M.E., Apperley, J.F., van Besien, K., Elmaagacli, A., Grigg, A., Reddy, V., Bacigalupo, A., Kolb, H.J., Bouzas, L., Michallet, M., Prince, H. M., Knobler, R., Parenti, D., Gallo, J. & Greinix, H.T. (2008) A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*, 112, 2667–2674.

(11) Seaton, E.D., Szydlo, R.M., Kanfer, E., Apperley, J. F. & Russell-Jones, R. (2003) Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. *Blood*, 102, 1217–1223.

(12) Foss, F.M., DiVenuti, G.M., Chin, K., Sprague, K., Grodman, H., Klein, A., Chan, G., Stiffler, K. & Miller, K.B. (2005) Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplantation*, 35, 1187–1193.

(13) Child, F.J., Ratnavel, R., Watkins, P., Samson, D., Apperley, J., Ball, J., Taylor, P. & Russell-Jones, R. (1999) Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GVHD). *Bone Marrow Transplantation*, 23, 881–887.

(14) Apisarnthanarax, N., Donato, M., Ko¨rbling, M., Couriel, D., Gajewski, J., Giralt, S., Khouri, I., Hosing, C., Champli, N.R., Duvic, M. & Anderlini, P. (2003) Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graftversus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transplantation*, 31, 459–465

(15) Messina, C., Locatelli, F., Lanino, E., Uderzo, C., Zacchello, G., Cesaro, S., Pillon, M., Perotti, C., Del Fante, C., Faraci, M., Rivabella, L., Calore, E., De Stefano, P., Zecca, M., Giorgiani, G., Brugiolo, A., Balduzzi, A., Dini, G., Zanesco, L. & Dall'Amico, R. (2003) Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. *British Journal of Haematology*, 122, 118–127.

References (2/5)

(16) Weitz M, Strahm B, Meerpohl JJ et al. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. *The Cochrane Library.* 2015;12

(17) Abu-Dalle I, Reljic T, Nishihori T et al. Extracorporeal Photopheresis in Steroid-Refractory Acute or Chronic Graft-versus-Host Disease: Results of a Systematic Review of Prospective Studies. *Biol Blood Marrow Transplant*. 2014; 20: 1677-1686

(18) Das Gupta E, Greinix H, Jacobs R et al. Extracorporeal photopheresis as second-line treatment for acute graft-versus-host disease: impact on six-month freedom from treatment failure, *Haematologica*. 2014; 99(11): 1746

(19) Rubegni P, Feci L, Poggiali S, et al. Extracorporeal photopheresis: a useful therapy for patients with steroid-refractory acute graft-versus-host disease but not for the prevention of the chronic form. *BJD*. 2013;169:450-457

(20) Ussowicz M, Musiał J, Mielcarek M et al. Steroid-Sparing Effect of Extracorporeal Photopheresis in the Therapy of Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation. *Transplantation Proceedings*. 2013; 45, 3375-3380

(21) Reddy, P.& Ferrara, J.L. (2003) Immunobiology of acute graft-versus-host disease. *Blood Reviews,* **17**, 187-94.

(22) Hattori, K., Hirano,T., Miyajima, H., Yamakawa, N., Tateno, M., Oshimi, K, Kayagaki, N., Yagita, H. & Okumura, K.. (1998) Differential effects of anti-Fas ligand and anti-tumor necrosis factor alpha antibodies on acute graft-versus-host disease pathologies. *Blood*, **91**:4051-5.

(23) Patriarca, F., Sperotto, A., Damiani, D., Morreale, G., Bonifazi, F., Olivieri, A., Ciceri, F., Milone, G., Cesaro, S., Bandini, G., Dini, G., Corradini, P. & Fanin, R. (2004) Infliximab treatment for steroid-refractory acute graft-versus-host disease. *Haematologica*, **89**, 1352-9.

(24) Couriel, D., Saliba, R., Hicks, K., Ippoliti, C., de Lima, M., Hosing, C., Khouri, I., Andersson, B., Gajewski, J., Donato, M., Anderlini, P., Kontoyiannis, D.P., Cohen, A., Martin, T., Giralt, S.& Champlin, R. (2004) Tumor necrosis factor-alpha blockade for the treatment of aGvHD. *Blood,* **104**, 649-54.

(25) Kobbe, G., Schneider, P., Rohr, U., Fenk, R., Neumann, F., Aivado, M., Dietze, L., Kronenwett, R., Hünerlitürkoglu, A.& Haas, R. (2001) Treatment of severe steroid refractory acute graft-versus-host disease with infliximab, a chimeric human/mouse antiTNFalpha antibody. *Bone Marrow Transplantation,* **28**, 47-9.

(26) Hervé, P., Flesch, M., Tiberghien, P., Wijdenes, J., Racadot, E., Bordigoni, P., Plouvier, E., Stephan, J.L., Bourdeau, H.& Holler, E. (1992) Phase I-II trial of a monoclonal anti-tumor necrosis factor alpha antibody for the treatment of refractory severe acute graft-versus-host disease. *Blood,* **79**, 3362-8.

(27) Marty, F.M., Lee, S.J., Fahey, M.M., Alyea, E.P., Soiffer, R.J., Antin, J.H.& Baden, L.R. (2003) Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. *Blood,* **102**, 2768-76.

(28) Pidala, J., Kim, J., Field, T., McBride, A., Kharfan-Dabaja, M., Perkins, J., Fernandez, H., Perez, L., Ayala, E.& Anasetti, C. (2009) Infliximab for managing steroid-refractory acute graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **15**, 1116-21.

(29) Couriel, D.R., Saliba, R., de Lima ,M., Giral, S., Andersson, B., Khouri, I., Hosing, C., Ippoliti, C., Shpall, E.J., Champlin, R.& Alousi, A. (2009) A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. *Biology of Blood and Marrow Transplantation,* **15**,1555-62.

(30) Yang, J., Cheuk, D. K. L., Ha, S. Y., Chiang, A. K. S., Lee, T. L., Ho, M. H. K., & Chan, G. C. F. (2012). Infliximab for steroid refractory or dependent gastrointestinal acute graft-versus-host disease in children after allogeneic hematopoietic stem cell transplantation. *Pediatric transplantation*, *16*(7), 771-778.

(31) Sieper, J.& Van Den Brande, J. (2005) Diverse effects of infliximab and etanercept on T lymphocytes. *Seminars in Arthritis and Rheumatism*, **34**, 23-7.

(32) Uberti, J.P., Ayash, L., Ratanatharathorn, V., Silver, S., Reynolds, C., Becker, M., Reddy, P., Cooke, K.R., Yanik, G., Whitfield, J., Jones, D., Hutchinson, R., Braun, T., Ferrara, J.L. & Levine, J.E.(2005) Pilot trial on the use of etanercept and methylprednisolone as primary treatment for acute graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **11**, 680-7.

(33) Levine, J.E., Paczesny, S., Mineishi, S., Braun, T., Choi, S.W., Hutchinson, R.J., Jones, D., Khaled, Y., Kitko, C.L., Bickley, D., Krijanovski, O., Reddy, P., Yanik, G.& Ferrara, J.L.(2008) Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. *Blood*, **111**, 2470-5.

References (3/5)

(34) Busca, A., Locatelli, F., Marmont, F., Ceretto, C.& Falda, M. (2007) Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. *American Journal of Hematology.* **82**,45-52.

(35) Han Park J, Jung Lee H, Rhan Kim S et al. Etanercept for steroid-refractory acute graft versus host disease following allogeneic hematopoietic stem cell transplantation. *Korean J Intern Med* 2014;29:630-636

(36) Bay, J.O., Dhédin ,N., Goerner, M., Vannier, J.P., Marie-Cardine, A., Stamatoullas, A., Jouet, J.P., Yakoub-Agha, I., Tabrizi, R., Faucher,C., Diez-Martin, J.L., Nunez, G., Parody, R., Milpied, N., Espérou, H., Garban, F., Galambrun, C., Kwiatkovski, F., Darlavoix, I., Zinaï, A., Fischer, A., Michallet, M. & Vernant JP. (2005) Inolimomab in steroid-refractory acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation: retrospective analysis and comparison with other interleukin-2 receptor antibodies. *Transplantation*, **80**, 782-8.

(37) Piñana, J.L., Valcárcel, D., Martino, R., Moreno, M.E., Sureda, A., Briones, J., Brunet, S. & Sierra, J. (2006) Encouraging results with inolimomab (anti-IL-2 receptor) as treatment for refractory acute graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **12**, 1135-41.

(38) Hale, G.(2001) The CD52 antigen and development of the CAMPATH antibodies. *Cytotherapy*, **3**, 137-43.

(39) Varadi, G., Or, R., Slavin, S. & Nagler, A.(1996) In vivo CAMPATH-1 monoclonal antibodies: a novel mode of therapy for acute graft-versus-host disease. *American Journal of Hematology*, **52**, 236-7.

(40) Carella, A.M., Beltrami, G., Scalzulli, P.R., Carella, A.M. Jr & Corsetti, M.T. (2004) Alemtuzumab can successfully treat steroid-refractory acute graft-versus-host disease (aGvHD). *Bone Marrow Transplantation*, **33**, 131-2.

(41) Wandroo, F., Auguston, B., Cook, M., Craddock, C.& Mahendra, P. (2004) Successful use of Campath-1H in the treatment of steroid refractory liver GvHD. *Bone Marrow Transplantation*, **34**, 285-7.

(42) Gómez-Almaguer, D., Ruiz-Argüelles, G.J., del Carmen Tarín-Arzaga, L., González-Llano, O., Gutiérrez-Aguirre, H., Cantú-Rodríguez, O., Jaime-Pérez, J., Carrasco-Yalán, A.& Giralt, S. (2008) Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **14**, 10-15.

(43) Schnitzler, M., Hasskarl, J., Egger, M., Bertz, H.& Finke, J. (2009) Successful treatment of severe acute intestinal graft-versus-host resistant to systemic and topical steroids with alemtuzumab. *Biology of Blood and Marrow Transplantation*, **15**, 910-8.

(44) Martínez, C., Solano, C., Ferrá, C., Sampol, A., Valcárcel, D.& Pérez-Simón, J.A.; Spanish Group for Stem Cell Transplantation (Grupo Español de Trasplante Hemopoyético y Terapia Celular). (2009) Alemtuzumab as treatment of steroid-refractory acute graft-versus-host disease: results of a phase II study. *Biology of Blood and Marrow Transplantation*, **15**, 639-42.

(45) Meunier M, Bulabois C, Thiebaut-Bertrand A, et al. Alemtuzumab for Severe Steroid-Refractory Gastrointestinal Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2014; 20: 1435-1454

(46) Khandelwal P, Lawrence J, Filipovich AH et al.The successful use of alemtuzumab for treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. *Pediatr Transplantation* 2014: 18: 94–102

(47) Margolis, J.& Vogelsang, G. (2000) An old drug for a new disease: pentostatin (Nipent) in acute graft-versus-host disease. *Seminars in Oncology*, **27**, 72-7.

(48) Foss, F.M. (2006) The role of purine analogues in low-intensity regimens with allogeneic hematopoietic stem cell transplantation. *Seminars in Hematology*. **43**, S35-43.

(49) Bolaños-Meade, J., Jacobsohn, D.A., Margolis, J., Ogden, A., Wientjes, M.G., Byrd, J.C., Lucas, D.M., Anders, V., Phelps, M., Grever, M.R. &Vogelsang, G.B. (2005) Pentostatin in steroid-refractory acute graft-versus-host disease. *Journal of Clinical Oncology,* **23**, 2661-8.

References (4/5)

(50) Pidala, J., Kim, J., Roman-Diaz, J., Shapiro, J., Nishihori, T., Bookout, R., Anasetti, C. & Kharfan-Dabaja MA. (2010) Pentostatin as rescue therapy for glucocorticoid-refractory acute and chronic graft-versus-host disease. *Annals of Transplantation*, **15**, 21-9.

(51) Alousi, A.M., Weisdorf, D.J., Logan, B.R., Bolaños-Meade, J., Carter, S., Difronzo, N., Pasquini, M., Goldstein, S.C., Ho, V.T., Hayes-Lattin, B., Wingard, J.R., Horowitz, M.M. & Levine, J.E. Blood and Marrow Transplant Clinical Trials Network (2009) Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. *Blood,* **114**, 511-7.

(52) Klein, S.A., Bug, G., Mousset, S., Hofmann, W.K., Hoelzer, D., Martin, H. (2011) Long term outcome of patients with steroid-refractory acute intestinal graft versus host disease after treatment with pentostatin. *British Journal of Haematology,* **154**, 143-6.

(53) Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., Moorman, M.A., Simonetti, D.W., Craig, S. & Marshak, D.R. (1999) Multilineage potential of adult human mesenchymal stem cells. *Science*, **284**, 143-7.

(54) Majumdar, M.K., Thiede, M.A., Haynesworth, S.E., Bruder, S.P.& Gerson, S.L. (2000) Human marrow-derived mesenchymal stem cells (MSCs) express hematopoietic cytokines and support long-term hematopoiesis when differentiated toward stromal and osteogenic lineages. *Journal of Hematotherapy and Stem Cell Research*, **9**, 841-8.

(55) Le Blanc, K., Rasmusson, I., Sundberg, B., Götherström, C., Hassan, M., Uzunel, M.& Ringdén, O. (2004) Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *Lancet*, **363**, 1439-41.

(56) Le Blanc, K., Frassoni, F., Ball, L., Locatelli, F., Roelofs, H., Lewis, I., Lanino, E., Sundberg, B., Bernardo, M.E., Remberger, M., Dini, G., Egeler, R.M., Bacigalupo, A., Fibbe, W. & Ringdén, O. (2008) Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Developmental Committee of the European Group for Blood and Marrow Transplantation. *Lancet*, **371**, 1579-86.

(57) Karlsson, H., Samarasinghe, S., Ball, L.M., Sundberg, B., Lankester, A.C., Dazzi, F., Uzunel, M., Rao, K., Veys, P., Le Blanc, K., Ringdén, O.& Amrolia, P.J. (2008) Mesenchymal stem cells exert differential effects on alloantigen and virus-specific T-cell responses. *Blood,* **112**, 532-41.

(58) Prasad, V.K., Lucas ,K.G., Kleiner, G.I., Talano, J.A., Jacobsohn, D., Broadwater, G., Monroy, R.& Kurtzberg, J. (2011) Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal™) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. *Biology of Blood and Marrow Transplantation,* **17**, 534-41.

(59) Martin, P.J., Uberti, J.P., Soiffer R.J., Klingemann H., Waller E.K., Daly A.S. Herrmann R.P., Kebriaei P.,(2010) Prochymal Improves Response Rates In Patients With Steroid-Refractory Acute Graft Versus Host Disease (SR-GVHD) Involving The Liver And Gut: Results Of A Randomized, Placebo-Controlled, Multicenter Phase III Trial In GVHD *Biology of Blood and Marrow Transplantation,* **16,** S169-S170.

(60) Kebriaei, P., Isola, L., Bahceci, E., Holland, K., Rowley, S., McGuirk, J., Devetten, M., Jansen, J., Herzig, R., Schuster, M., Monroy, R.& Uberti, J. (2009) Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. *Biology of Blood and Bone Marrow Transplantation*, **15**, 804-11.

(61) Pérez-Simon JA, López-Villar O, Andreu EJ, Rifón J, Muntion S, Campelo MD, Sánchez-Guijo FM, Martinez C, Valcarcel D, Cañizo CD. (2011) Mesenchymal stem cells expanded in vitro with human serum for the treatment of acute and chronic graft-versus-host disease: results of a phase I/II clinical trial. *Haematologica*. 96,1072-6.

(62) Jacobsohn, D.A., Chen, A.R., Zahurak, M., Piantadosi, S., Anders, V., Bolan˜os-Meade, J., Higman, M., Margolis, J., Kaup, M. & Vogelsang, G.B. (2007) Phase II study of pentostatin in patients with corticosteroid-refractory chronic graft-versus-host disease. *Journal of Clinical Oncology*, 25, 4255–4261.

(63) Jacobsohn, D.A., Gilman, A.L., Rademaker, A., Browning, B., Grimley, M., Lehmann, L., Nemecek, E.R., Thormann, K., Schultz, K.R. & Vogelsang, G.B. (2009) Evaluation of pentostatin in corticosteroid-refractory chronic graft-versushost disease in children: a Pediatric Blood and Marrow Transplant Consortium study. *Blood*, 114, 4354–4360.

References (5/5)

(64) Wolff, D., Schleuning, M., von Harsdorf, S., Bacher, U., Gerbitz, A., Stadler, M., Ayuk, F., Kiani, A., Schwerdtfeger, R., Vogelsang, G.B., Kobbe, G., Gramatzki, M., Lawitschka, A., Mohty, M., Pavletic, S.Z., Greinix, H. & Holler, E. (2011) Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biology of Blood and Marrow Transplantation*, 17, 1–17.

(65) Ratanatharathorn, V., Carson, E., Reynolds, C., Ayash, L.J., Levine, J., Yanik, G., Silver, S.M., Ferrara, J.L. & Uberti, J.P. (2000) Anti-CD20 chimeric monoclonal antibody treatment of refractory immune-mediated thrombocytopenia in a patient with chronic graft-versus-host disease. *Annals of Internal Medicine*, 133, 275–279.

(66) Cutler, C., Miklos, D., Kim, H.T., Treister, N., Woo, S.B., Bienfang, D., Klickstein, L.B., Levin, J., Miller, K., Reynolds, C., Macdonell, R., Pasek, M., Lee, S.J., Ho, V., Soiffer, R., Antin, J.H., Ritz, J. & Alyea, E. (2006) Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood*, 108, 756–762.

(67) Kim, S.J., Lee, J.W., Jung, C.W., Min, C.K., Cho, B., Shin, H.J., Chung, J.S., Kim, H., Lee, W.S., Joo, Y.D., Yang, D.H., Kook, H., Kang, H.J., Ahn, H.S., Yoon, S.S., Sohn, S.K., Min, Y.H., Min, W.S., Park, H.S. & Won, J.H. (2010) Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicenter, phase II study. *Haematologica*, 95, 1935–1942.

(68) Zaja, F., Bacigalupo, A., Patriarca, F., Stanzani, M., Van Lint, M.T., Filı`, C., Scime`, R., Milone, G., Falda, M., Vener, C., Laszlo, D., Alessandrino, .E., Narni, F., Sica, S., Olivieri, A., Sperotto, A., Bosi, A., Bonifazi, F., Fanin, R. & GITMO (Gruppo Italiano Trapianto Midollo Osseo) (2007) Treatment of refractory chronic GVHD with rituximab: a GITMO study. *Bone Marrow Transplantation*, 40, 273–277.

(69) Mohty, M., Marchetti, N., El-Cheikh, J., Faucher, C., Fu¨rst, S. & Blaise, D. (2008) Rituximab as salvage therapy for refractory chronic GVHD. Bone Marrow Transplantation, 41, 909–911.

(70) von Bonin, M., Oelschla¨gel, U., Radke, J., Stewart, M., Ehninger, G., Bornhauser, M. & Platzbecker, U. (2008) Treatment of chronic steroid-refractory graft-versus-host disease with low-dose rituximab. *Transplantation*, 86, 875–879.

(71) Kharfan-Dabaja, M.A., Mhaskar, A.R., Djulbegovic, B., Cutler, C., Mohty, M. & Kumar, A. (2009) Efficacy of rituximab in the setting of steroidrefractory chronic graft-versus-host disease: a systematic review and meta-analysis. *Biology of Blood and Marrow Transplantation*, 15, 1005–1013.

(72) Giralt, S.A., Arora, M., Goldman, J.M., Lee, S.J., Maziarz, R.T., McCarthy, P.L., Sobocinski, K.A. & Horowitz, M.M. (2007) Chronic Leukemia Working Committee, Center for International Blood and Marrow Transplant Research. Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. *British Journal of Haematology*, 137, 461–467.

(73) Blanke, C. (2010) Current management of GISTs. *Clinical Advances in Hematology and Oncology*, 5, 334.

(74) Bonner, J.C. (2004) Regulation of PDGF and its receptors in fibrotic diseases. Cytokine & Growth Factor Reviews, 4, 255–273.

(75) Ghofrani, H.A., Seeger, W. & Grimminger, F. (2005) Imatinib for the treatment of pulmonary arterial hypertension. *New England Journal of Medicine*, 353, 1412–1413.

(76) Majhail, N.S., Schiffer, C.A. & Weisdorf, D.J. (2006) Improvement of pulmonary function with imatinib mesylate in bronchiolitis obliterans following allogeneic hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation*, 12, 789–791.

(77) Magro, L., Mohty, M., Catteau, B., Coiteux, V., Chevallier, P., Terriou, L., Jouet, J.P. & Yakoub-Agha, I. (2009) Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. *Blood*, 114, 719–722.

(78) Olivieri, A., Locatelli, F., Zecca, M., Sanna, A., Cimminiello, M., Raimondi, R., Gini, G., Mordini, N., Balduzzi, A., Leoni, P., Gabrielli, A. & Bacigalupo, A. (2009) Imatinib for refractory chronic graft-versus-host disease with fibrotic features. *Blood*, 114, 709–718.

(79) Stadler, M., Ahlborn, R., Kamal, H., Diedrich, H., Buchholz, S., Eder, M. & Ganser, A. (2009) Limited efficacy of imatinib in severe pulmonary chronic graft-versus-host disease. *Blood*, 114, 3718–3719.