

Diagnosis and management of chronic graft-versus-host disease

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Summary

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) has reviewed the available literature and made recommendations for the diagnosis and management of chronic graft-versus-host disease (GvHD). This guideline includes recommendations for the diagnosis and staging of chronic GvHD as well as primary treatment and options for patients with steroid-refractory disease. The goal of treatment should be the effective control of GvHD while minimizing the risk of toxicity and relapse.

Keywords: Chronic, graft-versus-host disease, transplant, management, diagnosis.

Summary of recommendations

- 1 Chronic graft-versus-host disease (GvHD) and overlap syndrome should be diagnosed primarily using clinical criteria, supported by biopsy when possible. (1B)
- 2 Chronic GvHD should be graded as mild, moderate or severe according to National Institutes of Health (NIH) consensus criteria (Filipovich *et al*, 2005). (1A)
- 3 All patients with signs or symptoms suggestive of chronic GvHD in one organ should be assessed for involvement of other organs. (1A)

- 4 Corticosteroids are recommended in the first line treatment of chronic GvHD. (1A)
- 5 An initial starting dose of 1 mg/kg prednisolone is recommended. (1B)
- 6 Calcineurin inhibitors may be helpful in the initial treatment of GvHD as a steroid-sparer. (2C)
- 7 Extracorporeal photopheresis (ECP) may be considered as a second line treatment in skin, oral or liver chronic GvHD. (1B)
- 8 ECP schedule should be fortnightly-paired treatments for a minimum assessment period of 3 months. (1C)
- 9 Mammalian target of rapamycin (mTOR) inhibitors are suggested as a second line treatment option in refractory chronic GvHD. (2C)
- 10 Pentostatin is suggested as a second line treatment option in refractory chronic GvHD. (2B)
- 11 Rituximab is suggested as a second line treatment option in refractory cutaneous or musculoskeletal chronic GvHD. (2B)
- 12 Imatinib is suggested as a second line treatment option in refractory pulmonary or sclerodermatous chronic GvHD. (2C)
- 13 ECP, imatinib and rituximab may be considered as third line treatment options in chronic GvHD involving other organs. (2C)
- 14 The following agents are suggested as third line treatment options in refractory chronic GvHD: mycophenolate mofetil, methotrexate, pulsed corticosteroids. (2C)
- 15 There is insufficient evidence, at present, to support recommendations to use the following agents in the management of chronic GvHD: cyclophosphamide, mesenchymal stem cells, thalidomide, retinoids, alemtuzumab, infliximab, etanercept, clofazimine, alefacept, daclizumab, basiliximab, hydroxychloroquine, thoraco-abdominal irradiation. (1C)

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- 16 Azathioprine is not recommended in the management of chronic GvHD due to the risk of oral malignancy. (1C)

Introduction

Chronic graft-versus-host disease (cGvHD) remains a major complication of allogeneic stem cell transplantation and is the leading cause of late non-relapse death (Lee *et al*, 2002). The prevalence varies from 25–80% in long-term survivors (Baird & Pavletic, 2006). A clear diagnostic and management strategy for cGvHD has been difficult to achieve due to the polymorphic nature of the disorder and the paucity of evidence for the majority of treatment options. The National Institutes of Health (NIH) consensus development project has tried to address this issue by developing criteria for clinical trials in cGvHD (Filipovich *et al*, 2005; Couriel *et al*, 2006a; Martin *et al*, 2006; Pavletic *et al*, 2006; Schultz *et al*, 2006; Shulman *et al*, 2006). Similarly, the German-Austrian-Swiss working party on bone marrow and blood stem cell transplantation held a consensus conference to define clinical management of cGvHD in 2009 and have recently published several papers, including a summary of first- and second-line management of cGvHD (Wolff *et al*, 2010, 2011).

At present there are no UK guidelines on the diagnosis and management of cGvHD. T-cell depletion is used widely in the UK and this practice may have an impact on the frequency and pattern of cGvHD and, therefore, management guidelines from other countries may be less applicable in this setting. This document attempts to provide a summary of an evidence-based approach to the diagnosis, staging and management of cGvHD in clinical practice. The diagnosis and management of acute GvHD is discussed in a separate document (Dignan *et al*, 2012a) and the organ-specific management and supportive care of patients with GvHD is also discussed in a separate document (Dignan *et al*, 2012b). These guidelines are designed to be used together and to complement each other in order to provide an evidence-based approach to managing this complex disorder.

Methodology

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation followed by literature review to 17th June 2011 including Medline, internet searches and major conference reports.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies some recommendations are based on literature review and a consensus of expert opinion.
- The GRADE nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.

The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guideline pack and the GRADE working group website. See Appendix I. Further information is available from the following websites:

- o http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
- o <http://www.gradeworkinggroup.org/index.htm>

- Review by the BCSH committees, British Society of Blood and Marrow Transplantation (BSBMT) executive committee, the UK Photopheresis Society and the UK Paediatric Bone Marrow Transplant Group
- Review by sounding board of the British Society for Haematology (BSH) and allogeneic transplant centres in the UK.

Diagnosis

Historically, cGvHD was defined as occurring more than 100 d after transplant. The NIH consensus conference proposed two subcategories for cGvHD, classic and overlap syndrome, based on clinical features rather than time of onset. This proposal recognized that classical features of cGvHD could occur within 100 d of transplant and that features of acute and cGvHD could occur together (Filipovich *et al*, 2005). Furthermore, there is now evidence that this classification has clinical validity (Jagasia *et al*, 2009).

The consensus conference also identified ‘diagnostic’ and ‘distinctive’ features of cGvHD. Diagnostic signs are clinical features that establish the diagnosis of cGvHD without the need for further investigations. Diagnostic manifestations include poikiloderma and lichen planus-like features of the skin, lichen planus in the mouth or genitals, fasciitis and joint contractures. Distinctive signs are clinical features not associated with acute GvHD but which would be insufficient to make the diagnosis of cGvHD unless supported by positive biopsy or laboratory findings. Distinctive findings include skin depigmentation, nail dystrophy, alopecia, xerostomia, mucocoeles, ulceration of the mouth, keratoconjunctivitis sicca and myositis. A full list of diagnostic and distinctive findings is detailed in the first report of the NIH consensus conference (Filipovich *et al*, 2005). Additional investigations are helpful in confirming the diagnosis of cGvHD in patients with distinctive features and excluding other conditions, e.g. infection or drug toxicities. The role of additional investigations is discussed in the organ-specific management document of these guidelines (Dignan *et al*, 2012b).

The new diagnostic definitions were designed for use in clinical trials and have yet to be fully validated in clinical practice. A recent report from a German, Austrian and Swiss consensus conference reported a high rate of acceptance of the new cGvHD subcategories and diagnostic classification (Greinix *et al*, 2011).

Recommendation

- **Chronic GvHD and overlap syndrome should be diagnosed primarily using clinical criteria, supported by biopsy when possible (1B).**

Grading

Chronic GvHD was originally staged as limited or extensive disease based on the observations in 20 patients in a retrospective review (Shulman *et al*, 1980). The NIH consensus development project on criteria for clinical trials in cGvHD has reviewed staging of cGvHD (Filipovich *et al*, 2005). This document proposed a new clinical scoring system on a four point scale (0–3) with 0 representing no involvement, 1 mild involvement (no significant impairment of daily living), 2 moderate involvement (significant impairment of daily living) and 3 representing severe impairment (major disability). Chronic GvHD may then be classified as mild, moderate or severe. Patients with involvement of one or two organs with a score of 1 and no pulmonary GvHD are classified as having mild cGvHD. Moderate cGvHD is defined as involvement of three organs with a score of 1, at least one organ with a score of 2 or pulmonary GvHD with a score of 1. Patients who have major disability resulting in a score of 3 in any organ or site or patients who have pulmonary GvHD scoring 2 or 3 would be classified as having severe cGvHD. This classification is discussed in detail in Filipovich *et al* (2005) and has been reviewed by Devergie (2008). It is recommended that all patients are scored using the NIH criteria (Filipovich *et al*, 2005) at 3 months following transplant. In patients diagnosed with GvHD, restaging using NIH criteria is recommended every 3 months.

Prognostic factors

The John Hopkins group showed in multivariate analysis that extensive (>50%) skin involvement, a platelet count of $<100 \times 10^9/l$ and progressive onset from acute GvHD were associated with poor prognosis (Akpek *et al*, 2001a). More recently, Arora *et al* (2011) reported a cGvHD risk score. Ten variables were identified as being significant in terms of overall survival and non-relapse mortality: age, prior acute GvHD, time from transplantation to cGvHD, donor type, disease status at transplantation, GvHD prophylaxis, gender mismatch, serum bilirubin, Karnofsky score and platelet count (Arora *et al*, 2011).

Recommendation

- **Chronic GvHD should be graded as mild, moderate or severe according to NIH consensus criteria (Filipovich *et al*, 2005) (1A).**
- **All patients with signs or symptoms suggestive of chronic GvHD in one organ should be assessed for involvement of other organs (1A).**

Principles of cGvHD treatment

A multi-disciplinary approach is mandatory. Patients may require joint care with specialist teams including the dermatology, ophthalmology, gastroenterology, gynaecology and rheumatology teams as well as intensive input from physiotherapists and occupational therapists. Topical treatments and supportive agents also have an important role in effective management of cGvHD and may be sufficient in those patients with mild disease. Detailed organ-specific management including diagnosis, topical treatment and supportive care are discussed in a separate document entitled 'Organ specific management and supportive care in GvHD' (Dignan *et al*, 2012b).

First line systemic treatment for cGvHD*Corticosteroids*

The NIH consensus conference recommended systemic treatment for moderate or severe GvHD (Filipovich *et al*, 2005). Corticosteroids have been used as first line treatment in cGvHD since the 1980s. Their effect is likely to be due to lympholytic effects and anti-inflammatory properties (Deeg, 2007). The standard dose used has been 1 mg/kg in studies of steroids alone or in combination with other agents (Sullivan *et al*, 1988a; Koc *et al*, 2002). There are no randomized studies comparing this dose to higher or lower steroid doses. Topical steroids may be used in conjunction with systemic steroids and may allow dose reduction in those patients with GvHD limited to the skin.

At present, there is no consistent tapering protocol for steroid reduction in the UK. The Seattle group have reported on an alternate day dosing regimen for tapering steroids. This regimen involved using a daily dose of 1 mg/kg for two weeks and subsequently tapering to 1 mg/kg on alternate days over 4 weeks if cGvHD is stable or improving. The initial report (Sullivan *et al*, 1988a) used this schedule in combination with ciclosporin. In a recent review, Lee & Flowers suggested a similar initial schedule of 1 mg/kg for 2 weeks and then reducing the dose by 25% each week, aiming for a dose of 1 mg/kg on alternate days after 6–8 weeks. In severe GvHD, this dose may be maintained for 2–3 months and then tapered by 10–20% per month for a total duration of 9 months. An alternative regimen is to miss out the period of stable dosing of 2–3 months and to taper the dose by 10–20% per month until a dose of 0.5 mg/kg is reached. A slower steroid taper is advised thereafter depending on clinical response (reviewed by Lee & Flowers, 2008). Although there are no randomized studies comparing an alternate day approach to daily administration of corticosteroids in this setting, it is likely from studies undertaken in other patient groups that this approach may reduce side effects while maintaining efficacy (Dumler *et al*, 1982; Jabs *et al*, 1996).

In patients who are receiving other immunosuppressive agents it is recommended that steroids are tapered first. Other immunosuppressive agents can be tapered one at a time over a 3–9 month period with dose reductions every 2–4 weeks depending on clinical response (Lee & Flowers, 2008). The median duration of immunosuppressive therapy is 2–3 years (Lee & Flowers, 2008).

Calcineurin inhibitors

Cyclosporin is commonly used in the prophylaxis of GvHD. Cyclosporin binds to cyclophilin and prevents generation of nuclear factor of activated T cells (NF-AT), which is a nuclear factor for initiating gene transcription for lymphokines including interleukin 2 and interferon gamma. This action leads to suppression of cytokine production and subsequent inhibition of T-cell activation (reviewed in Greinix, 2008). Early reports suggested a possible benefit of cyclosporin in the primary treatment of cGvHD (Sullivan *et al*, 1988a). One randomized trial has been performed comparing the use of cyclosporin and daily 1 mg/kg prednisolone to prednisolone alone in the initial management of cGvHD. This study included 287 evaluable patients who

had platelet counts $>100 \times 10^9/l$ at the start of treatment. The cumulative incidence of transplantation-related mortality at 5 years was 17% in the combination arm compared to 13% in those patients who received prednisolone alone. There was no difference in efficacy as assessed by the need for secondary therapy at 5 years (11% vs. 17%) or the median interval to discontinuation of immunosuppression (1.6 vs. 2.2 years). A combination regimen of cyclosporin and prednisolone may have a steroid-sparing effect and reduce the incidence of steroid-associated complications: 22% of patients in the prednisolone arm developed avascular necrosis compared to 13% in the combination arm (Koc *et al*, 2002). These results may not be applicable to all types of transplant as this study group had received myeloablative conditioning regimens and had all received bone marrow.

There are limited data on the role of calcineurin inhibitors in the treatment of patients with refractory cGvHD. A prospective study of 17 patients with refractory disease reported a response to tacrolimus in six patients (Tzakis *et al*, 1991). In a larger Phase 2 study including 26 evaluable patients with cGvHD, a response to tacrolimus was observed in 12 patients (Kanamaru *et al*, 1995). In a single arm, open-label Phase 2

Table I. Summary of the major toxicities of cGvHD treatments.

Treatment	Major toxicities	Reference
Corticosteroids	Infection, hypertension, poor glycaemic control, mood swings, osteoporosis, weight gain, growth impairment	Joint Formulary Committee (2011)
Calcineurin Inhibitors	Infection, renal impairment, thrombotic microangiopathy, hypertension	Koc <i>et al</i> (2002)
Mycophenolate mofetil	Infection, deranged liver function tests, gastrointestinal disturbance, haematotoxicity, relapse	Martin <i>et al</i> (2009) Onishi <i>et al</i> (2010)
Sirolimus	Thrombotic microangiopathy, hyperlipidaemia, haematotoxicity	Jurado <i>et al</i> (2007) Johnston <i>et al</i> (2005)
Thalidomide	Teratogenicity, peripheral neuropathy, constipation, thrombosis, fatigue	Koc <i>et al</i> (2000)
Azathioprine	Oral malignancies, pancytopenia	Curtis <i>et al</i> (2005)
Pentostatin	Infection, pancytopenia	Pidala <i>et al</i> (2010)
Methotrexate	Deranged liver function tests, cytopenias	Inagaki <i>et al</i> (2008) Huang <i>et al</i> (2005)
Hydroxychloroquine	Gastrointestinal, ocular toxicity, rashes	Gilman <i>et al</i> (2000)
Clofazimine	Skin pigmentation, gastrointestinal, methaemoglobinaemia	Lee <i>et al</i> (1997) Moreira <i>et al</i> (1998)
Cyclophosphamide	Haematological, infection, urothelial toxicity	Mayer <i>et al</i> (2005)
Extracorporeal photopheresis	Patients with poor vascular access require indwelling catheter, vaso-vagal episodes	Scarlsbrick (2009)
Alefacept	Infection	Shapira <i>et al</i> (2009)
Imatinib	Dyspnoea, fluid retention, pancytopenia, deranged liver function	Stadler <i>et al</i> (2009)
Rituximab	Infusional reactions/infection, progressive multifocal leucoencephalopathy	Kharfan-Dabaja <i>et al</i> (2009)
Alemtuzumab	Infusional reactions/infections especially opportunistic e.g. cytomegalovirus	Park <i>et al</i> (2009) Peleg <i>et al</i> (2007)
Infliximab	Infusional reactions/ infection	Sleight <i>et al</i> (2007)
Etanercept	Infection	Chiang <i>et al</i> (2002) Busca <i>et al</i> (2007)
Basiliximab	Infection/infusional reactions	Willenbacher <i>et al</i> (2001)
Thoraco-abdominal irradiation	Haematotoxicity	Robin <i>et al</i> (2005)
Retinoids	Teratogenicity, hyperlipidaemia, deranged liver function	Marcellus <i>et al</i> (1999)

study, 8/39 patients achieved a benefit of switching from ciclosporin to tacrolimus for refractory cGvHD (Carnevale-Schianca *et al*, 2000). Regular monitoring of levels is required when using calcineurin inhibitors to avoid toxicity.

Recommendations

- **Corticosteroids are recommended in the first line treatment of chronic GvHD (1A).**
- **An initial starting dose of 1 mg/kg prednisolone is recommended (1B).**
- **Calcineurin inhibitors may be helpful in the initial treatment of GvHD as a steroid sparer (2C).**

Second-line systemic treatment in cGvHD

A number of agents have been used as second- and third-line therapy for cGvHD. The role of these therapies in the systemic management of cGvHD will be discussed in the following sections. The authors acknowledge that it is difficult to conduct randomized controlled trials in cGvHD and that the management suggestions made in this guideline are based on the interpretation of limited data available at time of review and widespread expert opinion. Many of these agents have significant toxicities, which are summarized in Table I.

These agents may be helpful in the management of steroid-refractory disease or as steroid-sparing agents in patients who are steroid-dependent or intolerant to steroids. The definition of steroid-refractory disease varies between studies but may include progression on prednisolone at 1 mg/kg per day for two weeks, stable disease on ≥ 0.5 mg/kg per day of prednisolone for 4–8 weeks and inability to taper prednisolone below 0.5 mg/kg per day (Martin *et al*, 2006; Wolff *et al*, 2011).

Ideally, patients with steroid-refractory cGvHD should be entered in to clinical trials. Where this is not possible, the choice of agent is likely to depend on the toxicity profile, organ involvement, patient preference and availability. Some agents may be used in combination or sequentially depending on clinical judgement. As there are no established predictors of response, second line therapy should, where possible avoid the changing of more than one agent at a time, with assessment at 8–12 weeks. Where there is progression within a 4-week period alternative therapies can be considered, although patients with sclerotic skin disease are likely to take longer to demonstrate response.

Extracorporeal photopheresis

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; Dignan *et al*, 2011). Flowers *et al* (2008) published the first multicentre, randomized controlled, prospective Phase II trial of ECP in the treatment of patients with cGvHD. 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). 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).

A UK consensus statement on the use of ECP in cGvHD suggested that patients with cutaneous, mucous membrane and hepatic manifestations of GvHD should be given priority for treatment as it is particularly efficacious in this setting (Scarlsbrick *et al*, 2008). This consensus group recommended a treatment schedule of two ECP treatments on two consecutive days every 2 weeks with less frequent monthly treatment in those who respond (Scarlsbrick *et al*, 2008). No benefit has been demonstrated for more regular treatments (reviewed in Scarlsbrick *et al*, 2008; Foss *et al*, 2005). The median number of ECP cycles in a recent UK study was 15 (30 treatments) and the median duration of treatment was 330 d (Dignan *et al*, 2011).

Although a number of biomarkers have been reported to predict response to ECP, none have been clinically validated.

The proportions of immature CD19⁺ CD21⁻ B lymphocytes may predict the response to ECP in cGvHD (Kuzmina & Greinix, 2009). There is some evidence that the ECP-treated cell dose may correlate with ECP effect (Perseghin *et al*, 2007; Whittle *et al*, 2011). Abnormalities of B-cell homeostasis with increased B-cell activating factor (BAFF) have been noted in cGvHD, with evidence of normalization in ECP responders (Whittle & Taylor, 2011). The use of ECP is associated with improved outcomes in classic and overlap cGvHD (Jagasia *et al*, 2009).

ECP requires venous access, which is not always possible using peripheral veins. Central lines may be required with the attendant complications of infection and blockage (Scarlsbrick, 2009). Systemic infections requiring either oral or intravenous antibiotics are at least halved in patients receiving ECP for 12 months (personal observations, PCT). Other side effects are minimal and include vasovagal episodes and fatigue.

ECP facilities should be quality assured. ECP requires well-maintained and validated machines, specifically trained staff, as well as skilful overall management to ensure effective use of resources, a safe patient care pathway and achievement of desirable outcomes. Clinical standards for such a service should be identified and adhered to through a quality assurance programme.

It is suggested that ECP may be helpful as a second line treatment in steroid-refractory cGvHD involving the skin, mouth or liver. There is less data supporting the use of ECP in cGvHD involving other organs but it may have a role as a third line option. The authors acknowledge that this specialized form of therapy may not currently be uniformly available in the UK.

Mammalian target of rapamycin (mTOR) inhibitors

Sirolimus is a macrolide antibiotic that exerts its immunosuppressive effect by inhibiting cytokine-driven signalling pathways of the T cell via mTOR blockade and specifically inhibiting the progression of cells from the G1 phase to the S phase. Sirolimus has been used in combination with other immunosuppressive agents in the management of refractory cGvHD. A Phase 2 study reported an overall response rate of 63% [6/35 complete response, 16/35 partial response (defined as > 50% improvement in clinical manifestations)] in patients with steroid-resistant cGvHD when sirolimus was used in combination with tacrolimus and corticosteroids (Couriel *et al*, 2005). Four patients developed thrombotic microangiopathy and 77% had infectious complications. The median survival was 15 months. A similar Phase 2 study enrolled 19 patients (Johnston *et al*, 2005). Only 16 were evaluable for response because three had discontinued the sirolimus after less than one month's treatment due to toxicity. A partial response was defined as any improvement in symptoms. This study reported an initial clinical response in 15/16 evaluable patients. Adverse events included renal

impairment in four patients and haemolytic-uraemic syndrome in two patients and relapse in one patient, leading to discontinuation of sirolimus in six patients (Johnston *et al*, 2005). Sirolimus levels were not checked in all patients. Sirolimus was used in a retrospective study in patients with refractory disease in combination with either calcineurin inhibitors, MMF or prednisolone in 47 patients (Jurado *et al*, 2007). Clinical responses were seen in 81% (38/47) of patients. Eighteen had a complete response and 20 had a partial response (defined as improvement in 1 organ without evidence of progression in another). Survival was 54.7% at 3 years. Four patients developed thrombotic microangiopathy (Jurado *et al*, 2007).

Everolimus is an alternative mTOR inhibitor. In an abstract of a single centre retrospective analysis including 29 patients with steroid-resistant disease, responses were seen in 69% of patients (two complete responses) treated with everolimus without an additional calcineurin inhibitor. No patients developed thrombotic microangiopathy (Klink *et al*, 2008).

mTOR inhibitors are suggested for use as a second line treatment option in refractory cGvHD. They should be used with caution in combination with calcineurin inhibitors in view of the risk of thrombotic microangiopathy and trough levels should be monitored. Patients should also be monitored for hyperlipidaemia. Care should be taken to avoid toxicity due to interactions with other medications, particularly azoles (Wolff *et al*, 2011).

Pentostatin

Pentostatin is a nucleoside analogue and 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 Natural Killer cells. The drug also causes prolonged lymphopenia although it is not significantly myelosuppressive (Margolis & Vogelsang, 2000). 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). 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). 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).

Rituximab

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 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). 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). 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). Rituximab may be considered as a second line treatment of musculoskeletal and skin cGvHD or as a third line option in cGvHD involving other organs.

Imatinib

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 β (TGF-β) 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 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). 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 subse-

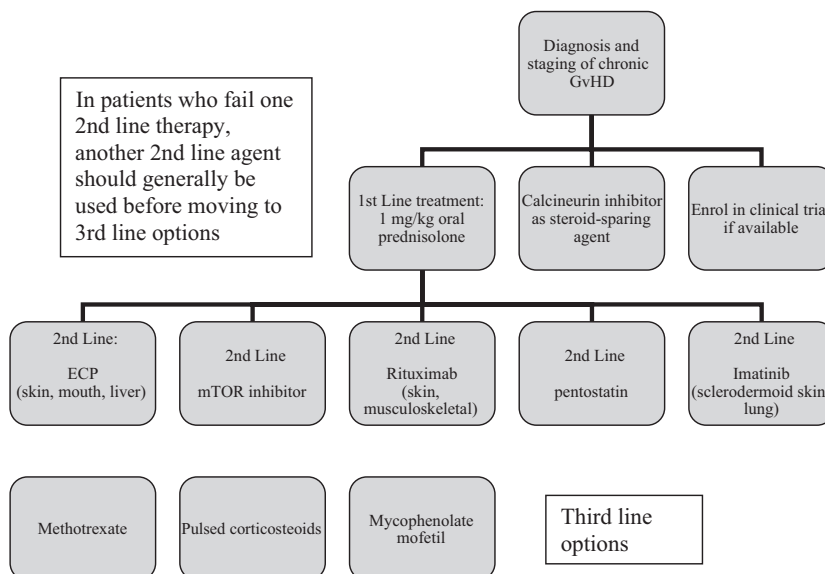


Fig 1. An algorithm to show 1st, 2nd and 3rd line treatment options in chronic GvHD. GvHD, graft-versus-host disease; ECP, extracorporeal photopheresis.

quently titrated to 400 mg if well tolerated. The role of imatinib in pulmonary GvHD is discussed in the organ-specific management and supportive care guideline (Dignan *et al*, 2012b). Imatinib may be used as a second line option for sclerodermoid or pulmonary cGvHD or as a third line option for cGvHD involving other organs.

Recommendations

- **Extra-corporeal photopheresis (ECP) may be considered as a second line treatment in skin, oral or liver chronic GvHD (1B).**
- **ECP schedule should be fortnightly-paired treatments for a minimum assessment period of 3 months (1C).**
- **Mammalian Target of Rapamycin (mTOR) inhibitors are suggested as a second line treatment option in refractory chronic GvHD (2C).**
- **Pentostatin is suggested as a second line treatment option in refractory chronic GvHD (2B).**
- **Rituximab is suggested as a second line treatment option in refractory cutaneous or musculoskeletal chronic GvHD (2B).**
- **Imatinib is suggested as a second line treatment option in refractory pulmonary or sclerodermatous chronic GvHD (2C).**
- **ECP, imatinib and rituximab may be considered as third line treatment options in chronic GvHD involving other organs (2C).**

Third line treatment options

A number of other agents have been investigated for the treatment of steroid-refractory disease. In patients who fail a second line treatment option another second line option should generally be considered before moving to a third line treatment option. Some agents may be used in combination but there is little data to support this approach. The agents that may be considered for third line treatment options are discussed below and shown in Fig. 1. These agents are considered to be third line options as there is less evidence available for their use. The authors acknowledge that some of these agents have not been studied in the context of third line treatment of cGvHD. All treatment options at this stage are likely to be associated with a high risk of infection.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is rapidly absorbed and hydrolysed to mycophenolic acid (MPA). MPA inhibits inosine monophosphate dehydrogenase, which blocks the *de novo* pathway of purine synthesis in lymphocytes and depletes the intracellular pool of guanosine triphosphate (Allison & Eugui, 2005). Martin *et al* (2009) performed a double-blind randomized controlled trial of MMF in the initial treatment

of cGvHD. Patients were receiving treatment with a calcineurin inhibitor or sirolimus and, in the majority of cases, prednisolone for cGvHD. Patients received MMF or placebo within 14 d of commencing systemic immunosuppression for cGvHD. The primary endpoint was resolution of cGvHD and withdrawal of all systemic treatment within two years but the study closed early as an interim analysis revealed a low probability of positive results for the primary endpoint (Martin *et al*, 2009). There was an estimated hazard ratio of death of 1.99 (95% confidence interval, 0.9–4.3) among patients in the MMF arm compared to the control arm. The majority of deaths in the MMF arm were due to infection or relapse and the authors concluded that MMF should not be added to the initial systemic treatment regimen for cGvHD.

There have been several small Phase 2 studies and case-series describing the possible efficacy of MMF in the management of refractory disease since the first report in 1999 (Mookerjee *et al*, 1999). Baudard *et al* (2002) reported a response rate of 69% in a retrospective study including 15 patients with cGvHD who were intolerant or had failed ciclosporin-containing regimens. A high rate of infectious complications was observed. Similarly, a response rate of 64% was reported in 7/11 paediatric patients with steroid-refractory disease in another retrospective series (Krejci *et al*, 2005). Takami *et al* (2006) prospectively evaluated five patients with refractory cGvHD and reported a 100% response rate. Lopez *et al* (2005) used MMF in 24 patients as a salvage/second line treatment and reported a 75% response rate. Similarly, Busca *et al* (2003) observed a response rate of 72% in 18 evaluable patients who had failed or were intolerant of standard immunosuppressive therapy. Another small study observed similar response rates but a high level of life-threatening infections (Onishi *et al*, 2010). Other common side effects included gastrointestinal disturbance and cytopenias. The effects of MMF can also mimic the appearance of intestinal GvHD on histopathological examination (Parfitt *et al*, 2008). Furlong *et al* (2009) undertook a prospective study of 23 patients treated with MMF for refractory cGvHD and reported disease resolution and discontinuation of immunosuppression in 26% of patients after 3 years of MMF treatment. The measurement of levels of MMF is useful to check absorption and prevent toxicity although these levels can be influenced by the serum albumin level (Hiwarkar *et al*, 2011).

Pulsed high-dose corticosteroids

Pulsed corticosteroids have been used in one study that included 61 patients with steroid-refractory disease (Akpek *et al*, 2001b). A dose of 10 mg/kg per day was given over 4 d followed by a course of additional immunosuppressive therapy. Forty-eight percent of patients showed a major response including softening of the skin, improved performance status or increased range of movement and an additional 27% showed a minor response (Akpek *et al*, 2001b). The regimen was

well tolerated but 50% of responders showed subsequent progression and only 27% of patients were able to discontinue immunosuppression at 2 years. The probability of survival at 2 years was 81%.

Methotrexate

Methotrexate, an antiproliferative agent, prevents the division and clonal expansion of T cells. The role of methotrexate is well established in the prophylaxis of GvHD and, due to its anti-inflammatory and antiproliferative properties, has been used extensively in the management of autoimmune disorders. Low-dose methotrexate has reported efficacy as an initial therapy in cGvHD. Wang *et al* (2009) reported on 86 patients who received methotrexate in combination with other immunosuppressive agents. Low dose intravenous methotrexate was well tolerated and the overall response rate was 83% (62% had a complete response); the highest response rates were observed in skin GvHD with 90% of patients responding (Wang *et al*, 2009). This study enrolled patients who had not received prior treatment for GvHD and the results cannot be extrapolated to patients with steroid-refractory disease.

Huang *et al* (2005) reported a response in 16/21 patients with cGvHD although reversible severe leucopenia was observed. de Lavallade *et al* (2006) reported a response in 6/8 patients with steroid-refractory cGvHD treated with an infusion of 5 mg/m² per week. Similarly, Giaccone *et al* (2005) reported a steroid-sparing effect in 14 patients using a dose of 7.5 mg/m² per weekly. Inagaki *et al* (2008) reported a retrospective analysis of 17 paediatric patients with steroid-refractory or steroid-dependent cGvHD who received 3–10 mg/m² weekly of methotrexate. Ten out of 17 patients (58.8%) responded. Grade III or IV toxicities occurred in six patients and included cytopenias or elevated levels of serum transaminases (Inagaki *et al*, 2008).

Recommendations

- **The following agents are suggested as third line treatment options in refractory chronic GvHD: mycophenolate mofetil, methotrexate, pulsed corticosteroids (2C).**

Other agents

A number of other agents have been investigated in the management of cGvHD. These therapies are discussed below although at present their use is not routinely recommended due to insufficient evidence or significant toxicity.

Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline antimalarial drug used in the treatment of autoimmune disorders. One Phase 2 trial has been undertaken using hydroxychloroquine for the

management of cGvHD (Gilman *et al*, 2000). This study included 40 patients with steroid-resistant or steroid-dependent cGvHD. Three complete responses and 14 partial responses were seen in 32 evaluable patients (20 children, 12 adults) and the best response were seen in skin, oral and liver disease (Gilman *et al*, 2000). The Children's Oncology Group recently performed a randomized double blind placebo controlled Phase 3 trial comparing standard of care to standard of care plus hydroxychloroquine, which unfortunately had to close early due to poor accrual. The complete response rate was 28% in the hydroxychloroquine arm compared to 33% in the placebo arm (Gilman *et al*, 2011).

Clofazimine

Clofazimine is an antimycobacterial drug that has anti-inflammatory properties and is used in the management of chronic skin disorders. One report of 22 patients with cGvHD observed a response rate of over 50% in patients with sclerodermoid skin GvHD, joint contractures or oral disease (Lee *et al*, 1997). Rzepecki *et al* (2007) reported partial or complete responses in four patients. There has been a case report of methaemoglobinaemia in a patient receiving clofazimine (Moreira *et al*, 1998).

Cyclophosphamide

Cyclophosphamide is a cytotoxic and immunosuppressive drug that is commonly used in pre-transplant conditioning regimens. There is one report of efficacy of cyclophosphamide in the management of GvHD (Mayer *et al*, 2005). This retrospective series included three patients with steroid-resistant cGvHD. Two patients had a complete response in liver GvHD and one had a response in oral GvHD (Mayer *et al*, 2005). High dose cyclophosphamide has also been used with 'pseudoautologous' stem cell rescue. This technique has led to improvement in cGvHD but with an associated risk of relapse (Pusic *et al*, 2002).

Alemtuzumab

Alemtuzumab is an unconjugated humanized IgG1 kappa monoclonal antibody that targets the CD52 antigen on the T and B lymphocytes as well as on monocytes, macrophages, eosinophils and dendritic cells (Giralt, 2006). Alemtuzumab has been used in the management of acute GvHD in several series (Carella *et al*, 2004; Wandroo *et al*, 2004; Busca *et al*, 2005). There is only one case report describing the use of alemtuzumab in the management of cGvHD, which reported resolution of refractory cutaneous cGvHD following administration of 10 mg/d alemtuzumab subcutaneously for six consecutive days every 4 weeks (Ruiz-Argüelles *et al*, 2008). The use of alemtuzumab is likely to significantly exacerbate the immunodeficiency associated with cGvHD.

Anti-tumour necrosis factor (TNF) antibodies

Infliximab is a chimeric human anti-TNF α -IgG1 κ monoclonal antibody that inhibits the binding of TNF to its cellular receptors. There are few reports of the efficacy of infliximab in the management of cGvHD. Rodriguez *et al* (2007) reported a response in one child with cGvHD of the liver treated with infliximab-daclizumab in combination. Sleight *et al* (2007) reported on a retrospective study that included six children with cGvHD treated with infliximab for steroid-resistant cGvHD. Five out of six children had a partial response but this was not sustained long-term. Gastrointestinal, oral and skin manifestations were most likely to respond.

Etanercept is a recombinant human soluble TNF α receptor fusion protein that inhibits TNF α . There are 2 reports detailing the use of etanercept in the management of cGvHD (Chiang *et al*, 2002; Busca *et al*, 2007). Both reports included eight patients with refractory cGvHD: Chiang *et al* (2002) reported responses in 7/8 evaluable patients and Busca *et al* (2007) reported a response in 5/8 patients.

Anti-TNF antibodies may be helpful in patients with overlap GvHD affecting the gut but there is limited evidence for their use in other manifestations of cGvHD at present.

Thoraco-abdominal irradiation

Low dose thoraco-abdominal irradiation has been used in the management of cGvHD due to its immunosuppressive and immunomodulatory properties. Bullorsky *et al* (1993) reported on three patients with refractory disease who obtained a response to total lymphoid irradiation. In a retrospective review of 41 patients with refractory cGvHD, 82% of patients achieved a clinical response to 1 Gray thoraco-abdominal irradiation (Robin *et al*, 2005). Overall survival at 10 years from irradiation was 57%.

Thalidomide

Thalidomide inhibits angiogenesis, expression of adhesion molecules, TNF α , interleukin 6, interleukin 12 and nuclear factor kappa B activity (Keifer *et al*, 2001; Lepper *et al*, 2006). A randomized clinical trial of thalidomide, ciclosporin and prednisolone compared to ciclosporin and prednisolone did not show any additional benefit in the primary treatment of cGvHD (Arora *et al*, 2001).

Several early studies reported thalidomide as a second line treatment in cGvHD. A complete or partial response was reported in 26/44 patients with cGvHD (Vogelsang *et al*, 1992). Similar results were reported by other investigators (Browne *et al*, 2000; Kulkarni *et al*, 2003). Rovelli *et al* (1998) reported a complete response rate in 6/14 children with refractory cGvHD. A higher response rate has been reported in patients with mucocutaneous disease (Parker *et al*, 1995).

Thalidomide has significant side effects including constipation, neuropathy, neutropenia, thrombocytopenia, tiredness

and thrombosis. In one trial using thalidomide as initial therapy, 92% of patients stopped the drug due to side effects (Koc *et al*, 2000). Starting at a low dose of 100 mg may help to minimize side effects (Wolff *et al*, 2011).

Alefacept

Alefacept is a dimeric anti-CD2 LFA-3 fusion protein that has been used in the management of acute and chronic GvHD (Toor *et al*, 2007; Shapira *et al*, 2009). Shapira *et al* (2009) reported a response in nine of 11 evaluable patients who received alefacept for refractory cGvHD. Six patients died due to progression of GvHD and infections.

Daclizumab/basiliximab

Daclizumab and basiliximab are monoclonal antibodies against the interleukin 2 receptor. There are few reports of their efficacy in the management of cGvHD. Willenbacher *et al* (2001) included four patients with cGvHD in their study of 16 patients; three out of four patients responded but they reported an increased incidence of infectious complications. Teachey *et al* (2006) reported that 2/4 children with cGvHD responded to daclizumab but noted that responses were only seen in skin GvHD. Daclizumab is no longer commercially available and basiliximab has not been studied in this context.

Retinoids

Retinoids have been used in several dermatological conditions and are known to interfere with collagen synthesis in fibroblasts, block the induction of T-helper 17 cells and promote the incidence of regulatory T cells. One study reported a response in 20/27 patients who received treatment with etretinate, a synthetic retinoid, for refractory sclerodermatous GvHD (Marcellus *et al*, 1999). Etretinate is not available in the UK but isotretinoin or acitretin might have a similar benefit. Ghoreschi *et al* (2008) reported a response in 4/5 patients with sclerodermoid cGvHD who received treatment with isotretinoin and psoralen + ultraviolet A (PUVA)-bath photochemotherapy.

Azathioprine

Azathioprine is an antimetabolite that exerts its effects after conversion to 6-mercaptopurine. It has been used in a double-blind randomized controlled trial comparing prednisolone alone to azathioprine in combination with prednisolone for early treatment of standard risk patients with cGvHD (Sullivan *et al*, 1988b). Non-relapse mortality was higher in the azathioprine group (40%) compared to the group receiving steroids alone (21%). Similarly, actuarial survival at 5 years was higher in the steroid group (61%) than in the combination group (47%). Azathioprine has also been associated with a higher incidence of oral malignancies (Curtis *et al*, 2005).

Mesenchymal stem cells (MSCs)

There are anecdotal reports of the use of MSCs in cGvHD and Weng *et al* (2010) recently reported a response rate of 74% in a series of 19 patients with cGvHD (Weng *et al*, 2010). At present, although they may be helpful in the management of acute GvHD, the role of MSCs in the management of cGvHD is less clear.

Recommendations

- **There is insufficient evidence at present to recommend the use of the following agents in the management of chronic GvHD: cyclophosphamide, MSCs, thalidomide, retinoids, alemtuzumab, infliximab, etanercept, clofazimine, alefacept, daclizumab, basiliximab, hydroxychloroquine, thoraco-abdominal irradiation (1C).**
- **Azathioprine is not recommended in the management of chronic GvHD due to the risk of oral malignancy (1C).**

Disclaimer

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Author contributions

FLD reviewed the literature and wrote the initial draft of the manuscript. MNP chaired the writing group, reviewed the literature and revised the manuscript. AC represented BCSH, reviewed the literature and revised the manuscript. GJ represented BSBMT, reviewed the literature and revised the manuscript. JS, JC, PA, PT, PM, and BES reviewed the literature and revised the manuscript.

Conflicts of interest

All authors have declared any potential conflicts of interest to BCSH. FLD and BES have received research funding,

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Appendix

GRADE nomenclature for assessing levels of evidence and providing recommendations in guidelines

Strength of recommendations. *Strong (Grade 1):* Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of evidence. The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) *High:* Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) *Moderate:* Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) *Low:* Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

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