bjh guideline

Diagnosis and management of chronic graft-versus-host disease

Fiona L. Dignan,[1,2] Persis Amrolia,[3] Andrew Clark,[4] Jacqueline Cornish,[5] Graham Jackson,[6] Prem Mahendra,[7] Julia J. Scarisbrick,[8] Peter C. Taylor,[9] Bronwen E. Shaw[1,10] and Michael N. Potter[1] on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation

[1]Section of Haemato-oncology, The Royal Marsden NHS Foundation Trust, London, [2]St John's Institute of Dermatology, St Thomas' Hospital, London, [3]Department of Bone Marrow Transplantation, Great Ormond Street Hospital, London, [4]Bone Marrow Transplant Unit, Beatson Oncology Centre, Gartnavel Hospital, Glasgow, [5]Department of Haematology, Bristol Royal Hospital for Children, Bristol, [6]Department of Haematology, Freeman Road Hospital, Newcastle, [7]Department of Haematology, University Hospital Birmingham, Birmingham, [8]Department of Dermatology, University Hospital Birmingham, Birmingham, [9]Department of Haematology, Rotherham General Hospital, Rotherham, and [10]Anthony Nolan, London, UK

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)

Correspondence: BCSH Secretary, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
E-mail: bcsh@b-s-h.org.uk

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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). Futhermore, 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, mucoceles, 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

Ciclosporin is commonly used in the prophylaxis of GvHD. Ciclosporin 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 ciclosporin in the primary treatment of cGvHD (Sullivan *et al*, 1988a). One randomized trial has been performed comparing the use of ciclosporin 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 × 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 ciclosporin 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 *et al* (2002)
Mycophenolate mofetil	Infection, deranged liver function tests, gastrointestinal disturbance, haematotoxicity, relapse	Martin *et al* (2009) Onishi *et al* (2010)
Sirolimus	Thrombotic microangiopathy, hyperlipidaemia, haematotoxicity	Jurado *et al* (2007) Johnston *et al* (2005)
Thalidomide	Teratogenecity, peripheral neuropathy, constipation, thrombosis, fatigue	Koc *et al* (2000)
Azathioprine	Oral malignancies, pancytopenia	Curtis *et al* (2005)
Pentostatin	Infection, pancytopenia	Pidala *et al* (2010)
Methotrexate	Deranged liver function tests, cytopenias	Inagaki *et al* (2008) Huang *et al* (2005)
Hydroxychloroquine	Gastrointestinal, ocular toxicity, rashes	Gilman *et al* (2000)
Clofazimine	Skin pigmentation, gastrointestinal, methaemoglobinaemia	Lee *et al* (1997) Moreira *et al* (1998)
Cyclophosphamide	Haematological, infection, urothelial toxicity	Mayer *et al* (2005)
Extracorporeal photopheresis	Patients with poor vascular access require indwelling catheter, vaso-vagal episodes	Scarisbrick (2009)
Alefacept	Infection	Shapira *et al* (2009)
Imatinib	Dyspnoea, fluid retention, pancytopenia, deranged liver function	Stadler *et al* (2009)
Rituximab	Infusional reactions/infection, progressive multifocal leucoencepthalopathy	Kharfan-Dabaja *et al* (2009)
Alemtuzumab	Infusional reactions/infections especially opportunistic e.g. cytomegalovirus	Park *et al* (2009) Peleg *et al* (2007)
Infliximab	Infusional reactions/ infection	Sleight *et al* (2007)
Etanercept	Infection	Chiang *et al* (2002) Busca *et al* (2007)
Basiliximab	Infection/infusional reactions	Willenbacher *et al* (2001)
Thoraco-abdominal irradiation	Haematotoxicty	Robin *et al* (2005)
Retinoids	Teratogenicity, hyperlipidaemia, deranged liver function	Marcellus *et al* (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 $\geq$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 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). 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 (Scarisbrick *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 (Scarisbrick *et al*, 2008). No benefit has been demonstrated for more regular treatments (reviewed in Scarisbrick *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.

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