REPORT

Consensus Conference on Clinical Practice in Chronic Graft-versus-Host Disease (GVHD): First-Line and Topical Treatment of Chronic GVHD

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Chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation is still associated with significant morbidity and mortality. First-line treatment of cGVHD is based on steroids of 1 mg/kg/day of prednisone. The role of calcineurin inhibitors remains controversial, especially in patients with low risk for mortality (normal platelets counts), whereas patients with low platelets at diagnosis and/or high risk for steroid toxicity may be treated upfront with the combination of prednisone and a calcineurin inhibitor. Additional systemic immunosuppressive agents, like thalidomide, mycophenolic acid, and azathioprine, failed to improve treatment results in the primary treatment of cGVHD and are in part associated with higher morbidity, and in the case of azathioprine, with higher mortality. Despite advances in diagnosis of cGVHD as well as supportive care, half of the patients fail to achieve a long-lasting response to first-line treatment, and infectious morbidity continues to be significant. Therefore, immunomodulatory interventions with low infectious morbidity and mortality such as photopheresis need urgent evaluation in clinical trials. Beside systemic immunosuppression, the use of topical immunosuppressive interventions may improve local response rates and may be used as the only treatment in mild localized organ manifestations of cGVHD.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) continues to be associated with significant morbidity and is the leading cause for late mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1,2]. Moreover, because of rising recipient age, and the use of unrelated donors as well as peripheral blood stem cells (PBSCs) as a graft source, the incidence of cGVHD has been increasing [3]. Although major progress has been achieved in understanding the pathophysiology of acute GVHD (aGVHD), cGVHD is far less defined. Current concepts include the persistence of alloreactive T cells, a Th1-Th2 shift of the cellular immune response, defective peripheral, and central tolerance mechanisms (ie, failure of control by regulatory T cells and/or impaired negative selection of T cells in the thymus), replacement of antigen presenting cells (APCs) of the host by APCs of the donor leading to indirect antigen presentation of allo-antigens, an increasing role of B cells producing auto- and allo-antibodies against the host, and unspecific mechanisms of chronic inflammation leading to fibrosis of involved organs [4]. First-line treatment of cGVHD consists mainly of prednisone with a starting dose of 1 mg/kg/day, often combined with a calcineurin inhibitor (CNI). Evidence for first-line treatment options is based on controlled trials with the exception of severe cGVHD, which continues to be associated with interior survival [1]. Until recently,

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no valid criteria for the diagnosis and staging of cGVHD severity were available, which limits the value of most reported trials on the treatment of cGVHD. The National Institutes of Health (NIH) consensus criteria on diagnosis and staging of cGVHD as well as on treatment response criteria, reported in 2005, provide defined criteria that should improve the validity of reported results on treatment of cGVHD in the future [5-9]. Despite available evidence from controlled studies, no consensus has been achieved on first-line treatment of cGVHD. The Consensus Conference on Clinical Practice in Chronic GVHD held in fall of 2009 in Regensburg, Germany (complete program provided at www.gvhd.de), aimed to summarize the current available evidence for first-line and topical treatment and to provide practical guidelines for the use of treatment modalities. The presented consensus was based on a review of published evidence and a survey on the current clinical practice including transplant centers from Germany, Austria, and Switzerland. Moreover, the consensus was circulated among all transplant centers performing allo-HSCT in Germany, Austria, and Switzerland, and was discussed during the Consensus Conference meetings. The Consensus Conference was organized under the auspices of the German working group on bone marrow and blood stem cell transplantation (DAG-KBT) and the German Society of Hematology and Oncology (DGHO), the Austrian Stem Cell Transplant Working Group of the Austrian Society of Hematology and Oncology, the Swiss Blood Stem Cell Transplantation Group (SBST), and the German-Austrian Paediatric Working Group on SCT.

The evaluation of evidence and the subsequent recommendation was graded according to the system used in grading of supportive care published by Couriel [10]. The evidence of the majority of treatment options in cGVHD is sparse, and, therefore, for most of the therapeutic options the strength of recommendation falls into category C. In addition, category C and evidence III level were further specified as shown in Tables 1 and 2. All recommendation and evidence levels were first rated by an expert panel and subsequently rated by all participants of the consensus process. Only evidence from the use in cGVHD was included in the evaluation.

According to the number and severity of organs involved with cGVHD, the NIH consensus defined mild cGVHD as mild involvement of 2 organs only, excluding lung involvement, moderate cGVHD as mild involvement of more than 2 organs, or moderate organ involvement excluding moderate lung involvement, and severe cGVHD as any severe organ manifestation or moderate lung manifestations [8].

Here, we discuss first-line and topical treatment options for cGVHD. We mainly focus on reported clinical trials and retrospective analyses. The literature search was performed by the working group on first-line treatment within the Consensus Conference using the Pubmed database. Only English literature was considered. Abstracts from the Bone Marrow Transplantation Tandem meetings, the European Bone Marrow Transplantation meetings, and the American Society of Hematology meetings were cited, but were not included in the evidence rating.

Table 1. Strength of Recommendation

Strength of Recommendation Level	Definition of Recommendation Level
A	Should always be offered
B	Should generally be offered
C	Evidence for efficacy is insufficient to support for or against, or evidence might not outweigh adverse consequences, or cost of the approach. Optional
C-1*	Use in first-line treatment justified
C-2*	Use in equal to or greater than second-line treatment justified
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.

*Only applied for topical treatment of chronic graft-versus-host disease (cGVHD).

Principles of First-Line Treatment of cGVHD

As the diagnosis of cGVHD has major consequences on the further clinical course of the patient, the diagnosis needs to be based on either diagnostic clinical signs of cGVHD or requires confirmation by histology as described by the NIH consensus as well as the consensus within the German/Austrian/Swiss Bone Marrow Transplantation Group [8]. Once diagnosis of GVHD is established, the first step is to distinguish classic cGVHD from overlap syndrome or late aGVHD. Especially in the latter situation as for overlap syndrome with dominating acute features, treatment should be applied according to standard practice in treatment of aGVHD (ie, treatment with steroids in

Table 2. Quality of Evidence Supporting the Recommendation

Strength of Evidence Level	Definition of Evidence Level
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from >1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from >1 center) or from multiple time series or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees
III-1*	Several reports from retrospective evaluations or small uncontrolled clinical trials
III-2*	Only 1 report from small uncontrolled clinical trial or retrospective evaluations
III-3*	Only case reports available

*Only applied for topical treatment of chronic graft-versus-host disease (cGVHD).

combination with a CNI). Standards for treatment of overlap syndrome with evenly balanced symptoms still need to be defined. While aGVHD is defined by the presence of exclusive features of aGVHD, the diagnosis of overlap syndrome is based on the simultaneous presence of symptoms of aGVHD and distinctive or diagnostic features of cGVHD [8]. The diagnosis of classic cGVHD requires the presence of either diagnostic or distinctive symptoms of cGVHD in the absence of features of aGVHD [8].

The Consensus Conference on Clinical Practice of Chronic GVHD focused on treatment of classic cGVHD. Prognostic features at diagnosis of cGVHD have been described. The presence of thrombocytopenia or direct progression from aGVHD have been associated with adverse outcome [1]. The value of "progressive onset" as a risk factor is limited by the fact that traditionally any GVHD being present at day 100 was documented as cGVHD. However, 2 studies reclassifying GVHD according to the NIH criteria revealed a significant proportion of patients being traditionally classified as cGVHD instead of late aGVHD [11,12]. The risk factor "thrombocytopenia" has been identified in cohorts receiving a myeloablative (MA) conditioning regimen and mainly bone marrow (BM) as a graft source [1]. Therefore, it remains to be shown whether low platelets remain as a risk factor in patients receiving nonmyeloablative regimens and PBSCs as a graft source. Additional risk factors are extensive skin disease (>50% body surface) as well as severe cGVHD (NIH grading) [1]. A detailed classification of cGVHD severity according to the NIH consensus is delineated in Table 3 [8].

As for treatment, prognosis of overlap syndrome is a matter of debate as well; Jagasia and colleagues [13] reported a significantly worse survival of patients with any features of aGVHD after day 100 of HSCT compared with cGVHD. This is in contrast to reports by Arora et al. [11] and Cho et al. [12], stating no significant survival difference in patients with overlap syndrome compared to classic cGVHD and to a retrospective analysis published by Vigorito et al. [14], demonstrating no significant survival differences between patients with late aGVHD and cGVHD.

Currently, no uniformly accepted definition of steroid refractory cGVHD is available. Generally, accepted criteria for steroid refractory cGVHD are (1) progression despite immunosuppressive treatment using 1 mg/kg/day of prednisone for 2 weeks, (2) stable disease if 4 to 8 weeks on ≥0.5 mg/kg/day of prednisone, and (3) inability to taper below 0.5 mg/kg/day of prednisone. Treatment duration may vary depending on clinical manifestation (sclerosis requires longer to respond) or toxicity (shorter duration in the presence of significant toxicity) [9,15]. In the presence of primary treatment failure, alternative treatment options need to be started.

Table 3. Severity Grading of cGVHD

Severity	Mild	Moderate	Severe
Number of involved organs	1-2	≥3	≥3
Severity of organ manifestations	1 (excluding lung)	2 (or lung 1)	3 (or lung 2)

Treatment of Mild cGVHD

During the Consensus Conference on Clinical Practice of Chronic GVHD, an agreement was achieved that mild cGVHD may be treated either with topical immunosuppressive agents or with systemic steroids alone. In the scenario of solely topical immunosuppression, a close follow-up and screening for any potential manifestation of cGVHD is crucial to detect systemic progression of cGVHD during topical treatment. An additional factor influencing the decision of treatment of choice is the risk for relapse of the underlying malignancy, supporting topical treatment in the presence of a high relapse risk.

In pediatric patients, 2 additional considerations have to be taken into account. Side effects of systemic steroid therapy can be deleterious on a growing child. On the other hand, patients with nonmalignant underlying diseases have no benefit from the cGVHD-associated graft-versus-leukemia (GVL) effect even in mild disease courses. Therefore, topical therapy should be offered as often and as early as possible.

Mild manifestations of cGVHD that cannot be sufficiently treated by topical treatment such as hepatic manifestations or fasciitis may be treated with systemic corticosteroids alone. Again, lower initial doses than 1 mg/kg/day of prednisone may be used, but evidence for or against a reduced dose of steroids is virtually absent. In the presence of a high risk of relapse, an approach using supportive treatment with either nonsteroidal anti-inflammatory drugs (involvement of fascia or joints) or ursodeoxycholic acid (hepatic disease) may be suitable treatment options as long as a close follow-up to detect progression is guaranteed.

Because treatment is rather symptomatic and does not aim to control a systemic process, topical treatment should be continued as long as symptoms are present and may be tapered and withdrawn in the presence of remission of symptoms. The same applies for systemic treatment, although treatment for at least 4 to 8 weeks should be given to avoid frequent relapses of symptoms of cGVHD.

Treatment of Moderate cGVHD: Role of Prednisone (A I)

Treatment of moderate cGVHD requires systemic immunosuppression. Additional topical treatment may be applied to speed up the response or to improve local response rates, but it does not replace the requirement

Table 4. First-Line Treatment Options in cGVHD

Agent	Recommendation (citation number of references)	Evidence	Side Effects	Comments
Steroids	A [16-18]	I	Osteoporosis, avascular necrosis of the bone, diabetes	Important but need to spare steroids because of side effect profile, generally sufficient in primary treatment of mild cGVHD as single agent, may be used in combination with CNI in moderate or severe cGVHD
CNI	C [16,17]	II	Renal toxicity, hypertension	Only be used in combination with steroids, spares steroids, lower rate of avascular necrosis of the bone, may be considered in combination with steroids in primary treatment of severe cGVHD as well as in CNI dependent moderate cGVHD
MMF in triple agent combinations	D [19]	II	GI complaints, infectious and relapse risk	Failure to improve efficacy in a randomized trial documented
Azathioprine	D [18]	II	Hematologic toxicity, infectious risk	Adverse outcome in a randomized trial in combination with steroids
Thalidomide	D [20,21]	II	Neurotoxicity, sedation, constipation, thrombosis	May be used in concomitant relapse of multiple myeloma

CNI indicates calcineurin inhibitors; MMF, mycophenolate mofetil; GI, gastrointestinal; cGVHD, chronic graft-versus-host disease.

for systemic immunosuppression. Standard treatment is 1 mg/kg/day of prednisone or an equivalent dose of methylprednisolone. So far, no other treatment option replacing steroids in first-line treatment has been evaluated, resulting in a grade A recommendation with an evidence grade of I, although a steroid-free approach has never been applied [16-18]. Steroid dependence of the majority of patients failing first-line treatment indicates the central role of steroids in treatment of cGVHD (Tables 4).

A first report in the early 1980s indicated that prednisone alone or in combination with other immunosuppressive agents (particularly azathioprine and cyclophosphamide) could improve the outcome of patients who required treatment for extensive cGVHD [66]. A randomized double-blinded study comparing

Table 5. Topical Immunosuppressive Treatment Options in cGVHD

Organ	Agent (citation number of references)	Recommendation	Evidence	Side Effects	Comments
Skin	Topical steroids [7]	C-1	III-1	Skin atrophy	Neck down: mid-strength steroids if no response upper strength steroids, face: hydrocortisone 1%
	Tacrolimus/Pimecrolimus [22-25]	C-1	III-1	Long-term risk for cutaneous malignancies	Should be given twice daily
	PUVA [26-31]	C-1	III-1	Phototoxicity, risk for cutaneous malignancies	Should not be used with phototoxic medication
	UVA [32-35]	C-1	III-1	Phototoxicity, risk for cutaneous malignancies	Requires no UV protection after treatment, should not be used with phototoxic medication
	UVB [36]	C-1	III-2	Phototoxicity, risk for cutaneous malignancies	Only effective in lichenoid cGVHD
GI	Topical steroids [37-39]	C-1	III-1		Either budesonide or beclomethasone
Lung	Topical steroids	B	III-2		May be combined with betamimetic agents
Oral	Topical steroids [40-44]	C-1	III-1-III-3	Best results with topical budesonide	Requires oral hygiene and possibly topical antifungals
	Topical tacrolimus /cyclosporine [45-51]	C-2	III-1	Burning	Potentially increases risk for oral malignancies, may be combined with topical steroids
	Topical PUVA/UVB [44,52-54]	C-2	III-1	Optional treatment option for refractory manifestations	Psoralene may be given topically or systemically
Eye	Topical steroids [55,56]	C-1	III-1	Risk for corneal thinning and infectious keratitis	Duration of exposure should be limited
	Topical cyclosporine [57-60]	C-1	III-1	Burning, stinging	Fewer long-term side effects compared to steroids, high long-term efficacy
Vaginal	Topical steroids [61-64]	B	III-3	Increased risk for infectious complications and atrophy	Topical estrogen application and antifungal prophylaxis suggested
	Topical tacrolimus/ cyclosporine/pimecrolimus [63-65]	B	III-3	Burning	Less well tolerated but better long-term efficacy

cGVHD indicates chronic graft-versus-host disease.

prednisone and placebo versus prednisone and azathioprine in patients with platelet counts >100,000/μL showed better outcome with prednisone alone, and thus established prednisone as the treatment of choice for patients with standard-risk extensive cGVHD [17]. The central role of prednisone was further confirmed by a randomized trial comparing prednisone alone versus prednisone and cyclosporine (CsA) in patients with extensive cGVHD and platelet counts >100,000/μL showing no difference in overall survival (OS) in the 2 arms and no better control of cGVHD [16].

Starting in the 1980s, the standard initial steroid dose for the treatment of cGVHD has been 1 mg/kg/day, regardless of whether prednisone was used alone or in combination with other drugs [17,18,66]. There are no randomized studies comparing this dose with higher or lower initial doses. Recent retrospective analyses of patients with aGVHD indicate that 1 mg/kg/day could be at least as effective as 2 mg/kg/day for patients with grades I-1I aGVHD [67]. Considering the need for protracted treatment of cGVHD, it may be worthwhile exploring lower doses of steroids. Pending such studies 1 mg/kg daily is considered the standard initial dose.

The Seattle group suggests to maintain this dose for 2 weeks and then to taper to 1 mg/kg every other day over a period of 6 to 8 weeks if symptoms are stable or improving, and then either maintain this dose for 2 to 3 months or continue straight on to taper by 10% to 20% per month [68]. The survey sent to all centers participating in the Consensus Conference revealed that 26 of 31 centers (84%) start to reduce the steroid dose after 2 weeks of treatment if symptoms are inactive. G. Vogelsang [15], from the Johns Hopkins group, reported that 90% of responding patients would have done so within 3 months after achieving the alternate-day dose; thus, a reevaluation of patients at this stage should guide further tapering. Patients with complete responses (CRs) should be further tapered 10% to 20% monthly, whereas those still responding should stay on 1 mg/kg for about another 3 months after achieving maximum response and then slowly be tapered as described. If symptoms flare during tapering, increasing the steroid dose may again induce response. Patients who by the 3-month reevaluation have not responded should be considered for alternative treatment strategies [15,68].

Since the early 1960s, alternate dosing of steroids has been considered an effective regimen for the treatment of many immune-mediated disorders. The dose-spacing is thought to maintain efficacy while reducing toxicity of the applied steroids [69]. However, there are no randomized studies comparing daily and alternate-day strategies in cGVHD. In kidney transplant patients, the alternate-day dosing reduces the level of plasma lipids [70]. Likewise, administration of steroids as a single dose in the morning instead of a split dose is meant to match the circadian cycle and reduce side effects. Randomized studies in children treated with prednisolone for nephrotic syndrome and adults treated for proctocolitis showed similar efficacy of single compared to split-dose strategies [71,72]. Whether this holds true for patients being treated for cGVHD still has to be demonstrated in prospective studies. There are no studies comparing the effects and side effects of prednisone to other systemic steroid preparations such as methylprednisolone in patients with cGvHD.

Role of CNIs (C II)

Although the role of steroids in first-line treatment is well established, the role of CNIs is less clear. The potential benefit of the CNIs CsA and tacrolimus (FK506) in the treatment of cGVHD has been addressed in a small number of studies [16,17]. In a nonrandomized trial conducted more than 20 years ago, Sullivan et al. [17] added an alternating-day schedule of CsA (6 mg/kg twice a day) to a previously established alternating-day regimen of 1 mg/kg prednisone to treat 40 high-risk patients with newly diagnosed multiorgan cGVHD and thrombocytopenia <100,000/μL. After 9 months a CR rate of 33% and 4-year survival of 51% were reported. These results compared favorably to a 16% CR and 26% survival rate of a cohort of 38 patients with cGVHD and thrombocytopenia treated by the same center in a similar period of time. This study constituted the basis for the inclusion of CNIs to the therapeutic regimens for cGVHD in clinical practice for many years [15,68,73].

However, this practice was challenged by a randomized trial, in which Koc and colleagues [16] compared CsA alternating with prednisone every other day to alternate-day prednisone alone in 287 patients with newly diagnosed cGVHD and a platelet count >100,000/μL [16]. The primary endpoint of this study was the incidence of treatment-related mortality (TRM) at 3 years, which was not different between both groups. There was also no significant difference with respect to the incidence of secondary therapy, the discontinuation of immunosuppression, the incidence of recurrent malignancy, or OS in this study. In contrast, patients treated with CsA and prednisone showed a significantly inferior survival without recurrent malignancy (progression-free survival [PFS]) compared to patients treated with prednisone alone. In addition, a small subset of high-risk patients with progressive onset cGVHD displayed a tendency for increased TRM and inferior survival at 5 years in the CsA plus prednisone (16 patients) versus the prednisone alone (29 patients) arm. A significantly decreased rate of avascular necroses in patients treated in the combination arm was observed, suggesting that the addition of CsA to the therapeutic regimen resulted in lower

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