Biol Blood Marrow Transplant 25 (2019) 1450–1455

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Changes in Immunosuppressive Treatment of Chronic Graft-versus-Host Disease: Comparison of 2 Surveys within Allogeneic Hematopoietic Stem Cell Transplant Centers in Germany, Austria, and Switzerland

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Article history:
Received 9 January 2019
Accepted 4 March 2019

Key Words:
Allogeneic hematopoietic stem cell transplantation
Chronic graft-versus-host disease
Immunosuppressive therapy
Bone marrow transplantation

A B S T R A C T

Chronic graft-versus-host disease (cGVHD) remains the leading cause of late morbidity and mortality. Despite the growing number of treatment options in cGVHD, evidence remains sparse. The German-Austrian-Swiss GVHD Consortium performed a survey on clinical practice in treatment of cGVHD among transplant centers in Germany, Austria, and Switzerland in 2009 and 2018 and compared the results. The survey performed in 2009 contained 20 questions on first-line treatment and related issues and 4 questions on second-line scenarios followed by a survey on all systemic and topic treatment options known and applied, with 31 of 36 transplant centers (86%) responding. The survey in 2018 repeated 7 questions on first-line treatment and 3 questions on second-line scenarios followed by an updated survey on all current systemic treatment options known and applied, with 29 of 66 centers (43%) responding. In summary, the results show a large overlap of first-line treatment practice between centers and the 2 surveys because of a lack of new data that changes practice, except significant heterogeneity of treatment of cGVHD progressive onset type, which can be explained by the lack of trials focusing on this high-risk entity. In contrast, treatment options applied to second-line therapy vary considerably, with new agents like ibrutinib and ruxolitinib entering clinical practice. Moreover, treatment of bronchiolitis obliterans syndrome demonstrates heterogeneity in applied therapeutic options and sequence because of a lack of controlled data and different conclusions from already existing evidence. In summary, the survey results demonstrate an increasing number of treatment options applied to cGVHD accompanied by a significant heterogeneity in second-line treatment and underline the urgent need for clinical trials and registry analyses on rare entities with high mortality like progressive onset type and lung involvement of cGVHD.

Financial disclosure: See Acknowledgments on page 1455.

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https://doi.org/10.1016/j.bbmt.2019.03.003
1083-8791/

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) remains the leading cause of long-term morbidity and mortality after allogeneic hematopoietic stem cell transplantation (alloHSCT) and impairs quality of life [1-3]. Because of the clinical impact, the National Institutes of Health proposed consensus guidelines for diagnosis and severity grading of GVHD within clinical trials [4-6], which have been included in clinical routine [7]. In contrast to the guidelines for diagnosis and staging of GVHD, guidelines for treatment of cGVHD are lacking, which is mainly because of the lack of controlled trials in salvage treatment [8]. In addition, only a limited number of randomized trials on first-line treatment of cGVHD have been performed on historic patient populations that cannot be easily transferred to the current clinical situation, did not target the question on the current role of calcineurin inhibitors (CNIs) in first-line treatment [9-11], or result in major changes in clinical practice [12-15]. An additional covariable is the growing number of new treatment options available, including the first US Food and Drug Administration (FDA)-approved drug for the treatment of steroid-refractory cGVHD, ibrutinib [8,16]. Consequently, clinical practice varies considerably between transplant centers.

To document the current practice and assess the impact of emerging new treatment options in cGVHD on daily practice, a survey among German, Austrian, and Swiss transplant centers was performed in 2018 that covered specific treatment decisions on first- and second-line treatment of cGVHD as well as an assessment of all treatments currently applied in clinical care of cGVHD. The results were compared with a survey performed in 2009 that included in part identical questions and responses from the same transplant centers. The results of the survey performed in 2009 have already been published in part within the consensus publications of the German-Austrian-Swiss GVHD Consortium [17-19].

METHODS

Survey 2009

A paper-and-pencil–based questionnaire written in German on current clinical practice of first-line, second-line, and topical treatment of cGVHD was sent electronically to 36 centers performing alloHSCT or providing long-term care after alloHSCT within Germany, Austria, and Switzerland. Within the survey the centers were asked for their approach to first-line and second-line treatment of cGVHD. The possible answers were provided in a multiple-choice format and an additional field for comments in case the provided answers did not match with the current practice. The survey was either sent to the chair of the alloHSCT program or the physician responsible for long-term care (in case of prior participation in activities of the German-Austrian-Swiss GVHD Consortium). Thirty-one of 36 transplant centers (86%) contacted responded to the 2009 survey. The centers that replied were as follows: Augsburg, Basel, Berlin (Benjamin Franklin, Mitte, and Virchow [children]), Cologne, Dresden, Duesseldorf, Essen, Erlangen, Freiburg, Greifswald, Göttingen, Hamburg, Hannover, Jena, Kiel, Linz, Muenster (adults and children), Munich (LMU and children), Nuernberg, Regensburg, Rostock, Tuebingen, Ulm, Vienna (adults and children), Wiesbaden, and Wuerzburg. Several transplantation centers stated using different treatment strategies for the same clinical scenarios. In the latter situation, each answer was counted separately.

Survey 2018

Again, a paper-and-pencil–based questionnaire on current clinical practice of first-line, second-line, and topical treatment of cGVHD was sent electronically to 66 centers performing alloHSCT within Germany, Austria, and Switzerland. Twenty-nine centers responded, representing 54% of German, 31% of Austrian, and 87% of Swiss (only German-speaking centers included) transplant activities. The centers that replied were as follows: Aachen, Basel, Berlin (Charite), Berlin Buch, Bremen, Dresden, Duesseldorf, Essen, Erlangen, Frankfurt (Main), Frankfurt (Oder), Freiburg, Graz, Hamburg (UKE), Hamburg (St. Georg), Hannover, Jena, Kiel, Leipzig, Mainz, Mannheim, Muenster (adults), Munich Schwabing, Nuernberg, Oldenburg, Regensburg, Vienna (Children), and Zuerich. Centers participating in the 2009 survey but lacking responses to the 2018 survey were contacted with a reminder e-mail and/or by call.

RESULTS

Question 1: How do initially treat mild cGVHD (mild organ involvement of 2 organs only excluding lung involvement) of organs that can be reached by topical treatment in the presence of low risk of relapse of the underlying malignancy?

In summary, most responding centers (21/31; 68%) from the 2009 survey stated the use of topical treatment options only in mild cGVHD. Three centers used either a combination of topical and systemic treatment with corticosteroids (CS) or topical treatment only. One center used solely systemic CS.

Question 2: How do you initially treat mild cGVHD of organs that cannot be reached by topical treatment (mild elevation of liver enzymes, mild stiffness of joints)?

Half of the centers (15/31) from the 2009 survey stated use of systemic CS with a dose < .5 mg/kg/day, whereas 14 of 31 centers stated using doses between .5 and 1 mg/kg/day. Seven centers stated using in part an alternative approach, with 1 center using extracorporeal photopheresis (ECP) only and 1 center combining cyclosporine (CsA) with mycophenolate mofetil (MMF) or ursodeoxycholic acid if liver involvement was present. One center stated using high-dose CS (>1 mg/kg/day). The first 2 questions were not repeated in the 2018 survey.

Question 3: How do you initially treat moderate cGVHD (erythema of the skin 18% to 49% body surface, moderate oral and mild liver involvement with normal platelets, and no progressive onset) in a patient with low risk of relapse of the underlying malignancy who are off immunosuppression at time of diagnosis of cGVHD?

The results of question 3 are depicted in Figure 1a. In the fourth question the same clinical scenario as in question 3 but with presence of low platelets at time of onset of cGVHD was described. The applied treatment options are shown in Figure 1b. Several centers added topical immunosuppression.

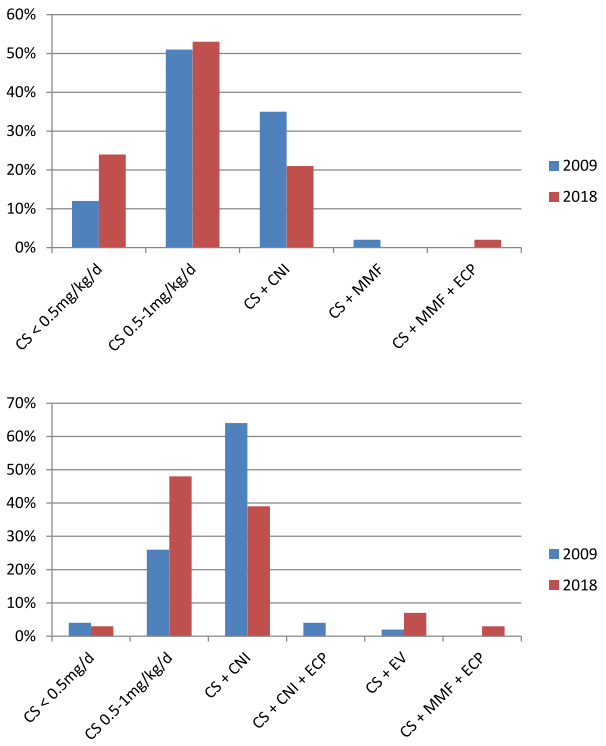

Figure 1. (A) First-line treatment of moderate cGVHD with normal platelets. (B) First-line treatment of moderate cGVHD with low platelets.

Question 5 to 8 from the 2009 survey asked for the type of CS, maximal dose, and circadian distribution used in treatment of cGVHD. Sixteen centers reported using prednisone, 7 methylprednisolone only, and 8 prednisone and methylprednisolone. Other types of CS were not used. Nineteen centers applied the CS dose once daily in the morning. Fifteen centers divided the CS dose into 2 doses given in the morning and at noon (n = 4) or in the morning and at night (n = 11). Two centers split the CS dose into 3 doses given in the morning, at noon, and at night. Three centers applied 2 different schedules and were counted twice. Six centers stated using daily application of CS until complete withdrawal. Seven centers attempted to use an every other day schedule at doses above .25 mg/kg/day CS, whereas 18 centers stated using an every other day schedule after dose reduction below .25 mg/kg/day. Several centers stated using an every other day schedule, especially after reaching doses below 10 mg after long exposure to CS. Twenty-five centers applied CS with an initial dose $\leq$ 1 mg/kg/day. Nine centers stated using initially higher doses for longer than 1 week (3 centers used both approaches). Ten centers stated using occasionally a pulse of CS (>2 mg/kg/day) for less than 1 week for rapid symptom control.

Question 9: A patient is initially treated for cGVHD involving liver (hepatitis) and skin with 1 mg/kg/day prednisone. After 2 weeks of treatment the skin rash disappeared and liver enzymes normalized. How do you continue immunosuppression?

Twenty-six centers stated starting reduction of the CS dose, whereas 4 centers would continue for another 4 weeks with a dose of 1 mg/kg/day of CS before dose reduction. One center would continue 1 mg/kg/day for at least 3 months after achieving remission of cGVHD before starting dose reduction.

The 10th question asked for a complete list of treatment potential options applied in first-line treatment of classic cGVHD excluding progressive onset type. The results are shown in Figure 2. Of note, in 2018 ruxolitinib (RUX) was reported for the first time by 1 center as potential option in first-line treatment and 9 centers would continue using CS and CNI only.

Question 11: How do you treat a patient with progressive onset of cGVHD during treatment of acute GVHD of the skin and gut (both are in remission) during taper of steroids on a dose of prednisone .5 mg/kg/day and CNI with moderate involvement of the skin, oral mucosa, and liver; low risk of relapse of the underlying malignancy; and platelets < 100/nL?

Within the 2009 survey most centers (18/31; 58%) stated they would increase the CS dose, continue the CNI, and start a new agent (MMF [n = 12; 39%], ECP [n = 9; 29%]). Two centers added an mTOR inhibitor (mTORi) or changed the CNI from CsA to tacrolimus (n = 1). In addition, the use of antibodies including rituximab and antithymocyte globulin was reported by single centers. Moreover, topical treatment with ultraviolet A light (UVA) or psoralen and ultraviolet A light (PUVA) was reported. Five centers (16%) continued CS and the CNI with the same dose and added MMF (n = 4; 13%) or ursodeoxycholic acid. Eight centers (26%) used an increased dose of CS only. Three centers would continue the same dose of CS, stop the CNI, and add either MMF or an mTORi or ECP. One center considered the use of alemtuzumab as a combination partner. Three centers would increase the CS dose, stop the CNI, and add either ECP (n = 2) or rituximab. One center considered the use of etanercept. The 2018 survey revealed slightly different results, with 6 centers increasing the CS dose only, 9 centers increasing CS and adding ECP, 3 centers adding MMF only, 1 center adding RUX, 2 centers switching the CNI to an mTORi and temporarily increasing CS, 1 center using either MMF or RUX, 3 centers using either ECP or RUX, 3 centers using either ECP or MMF, and 1 center adding MMF and ECP.

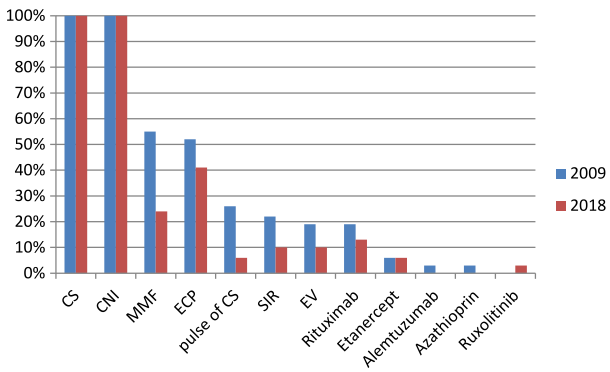

Figure 2. Applied first-line treatments in classic cGVHD without progressive onset.

Question 12 repeated the prior case of progressive onset but with normal platelets at diagnosis. Nine centers would increase the CS dose as the only therapeutic intervention and would continue the CNI. Nine centers (29%) would continue CNI and CS with the same dose and add MMF (n = 5; 16%), ECP (n = 4; 13%), everolimus (EV) (n = 1), antibodies including rituximab (n = 1), or infliximab (n = 1). Thirteen centers stated using an increased dose of CS, continuing the CNI, and starting either MMF (n = 10; 32%) or ECP (n = 5; 16%). Other treatment options added were methotrexate, rituximab, sirolimus, EV, antithymocyte globulin, as well as topical treatment with UVA or PUVA. One center would stop the CNI, continue the CS with the same dose, and would add an mTORi. An additional center would increase the CS dose, stop the CNI, and add either MMF or an mTORi. The 2018 survey revealed no major differences to the prior approach except increasing the use of ECP and declining the use of MMF, with 4 centers increasing the CS dose only, 10 centers (34%) adding ECP with a temporary increase of CS, 3 centers using either ECP or RUX, 1 center adding RUX only, 1 center using either MMF or RUX, 4 centers (14%) adding MMF, 1 center using either ECP, RUX, or MMF, and 2 centers using ECP or MMF. One center would not increase CS and add an mTORi, 1 center would switch the CNI to an mTORi, and 1 center would add MMF and ECP.

The next question of the 2009 survey was whether the transplant center would apply any standard policy in newly diagnosed progressive onset type of cGVHD involving skin, oral mucosa, liver, and low platelets. Twenty-one centers (68%) reported using an individualized approach, whereas 10 centers stated using a standardized approach.

The next 2 questions of the 2009 survey evaluated specifically the use of MMF in first-line treatment of cGVHD. Six centers stated having never used MMF in first-line treatment. One additional center stated stopping the use of MMF, 12 centers occasionally applied MMF to increase the response rate, whereas 3 centers reported the frequent use of MMF to increase the response rate. Eighteen centers applied MMF occasionally and 3 frequently to spare steroids. If MMF was used, 1 center applied MMF as a single-agent treatment and 17 centers combined it with CS. Eighteen centers combined prednisone, CNI, and MMF; 4 centers reported the combination of MMF with a CNI without additional CS; and 3 combined MMF with an mTORi or ECP, respectively.

The last question of the 2009 survey on first-line treatment explored the use of ECP and combination partners in first-line treatment of cGVHD. Twenty-eight of 31 centers (90%) reported using ECP. Twelve centers did not use ECP in first-line

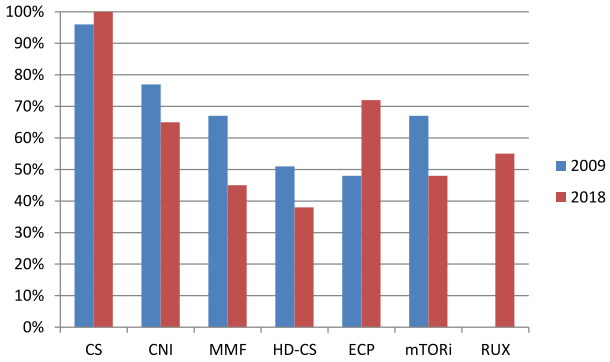

Figure 3. Most frequently applied systemic treatments of BOS comparing 2009 with 2018.

treatment, whereas 1 center used ECP as a single treatment strategy. Ten centers combined ECP with CS, 12 combined ECP with a CS and a CNI, and 3 with a CS and an mTORi. Within the 2018 survey 7 centers would not use ECP in first-line treatment. Four centers combined ECP with CS and 2 with CS and CNI. The remaining 15 centers reported multiple combinations, including ECP in combination with CNI and CS, mTORi, and MMF alone. Interestingly, 4 centers considered ECP as a single treatment option.

The next question evaluated the organ-specific approach in the treatment of bronchiolitis obliterans syndrome (BOS), including the treatment sequence within the 2009 and 2018 survey. The results are depicted in Figure 3, and sequence is provided in the Supplementary Appendix. In summary, in 2009 the most frequent applied treatments were CS (30/31), CsA (24/31), MMF (21/31), and ECP (15/31) followed by tacrolimus (13/31) and mTORi (11/31). The 2018 survey revealed slightly different results in part because azithromycin, inhalative CS, and montelukast [20] as well as RUX and ibrutinib were added to the list of agents. CS remained the most important treatment applied by all centers. In addition, an increasing use of ECP (21/29) and some decreasing use of MMF (13/29) were observed. Inhalative CS were used by all but 1 centers. In contrast, azithromycin was used by 25 of 29 centers only, and 1 additional center stated stopping the use of azithromycin after an FDA warning on an increased relapse rate after application in prophylaxis [21]. In contrast, montelukast was used by 20 of 29 only, and only 13 centers applied the complete montelukast regimen upfront.

The next 2 questions from the 2009 survey dealt with the role of inhalative treatment of BOS. Twenty-seven centers stated using the combination of inhalative and systemic CS, whereas 6 applied systemic CS only and 2 used both options. Four centers would not use any other inhalative treatment, whereas 7 would apply short-acting sympathomimetic inhalative agents. Twenty-four centers used long-acting sympathomimetic agents and 8 applied parasympatholytic agents. One center did not answer the second part of the question.

FIRST-LINE TREATMENT

The following question was on applied drug levels used for treatment of cGVHD:

- CsA: Baseline levels > 200 ng/mL were the aim of 1 center, 11 centers applied target levels of 151 to 200 ng/mL, whereas 17 centers applied target levels of 100 to 150 ng/mL. Lower mean levels were used by 1 center only.
- Tacrolimus: Baseline levels > 10 ng/mL were the aim of 2 centers, 7 applied levels of 7.6 to 10 ng/mL, and 11 levels from 5 to 7.5 ng/mL. Lower mean levels were used by 1 center only.
- Sirolimus: Baseline levels > 10 ng/mL were the aim of 2 centers, 3 had targeted levels of 7.6 to 10 ng/mL, whereas 9 centers used target levels of 5 to 7.5 ng/mL. Lower baseline levels were used by 1 center only.
- EV: Nine centers applied target drug levels of 5 to 7.5 ng/mL, whereas 4 used target levels below 5 ng/mL. Eighteen centers did not answer this question in part due to the lack of usage of mTORi.

SECOND- LINE TREATMENT

Questions regarding the second-line treatment of cGVHD are as follows:

A patient receives treatment with prednisone 1 mg/kg/day for de novo cGVHD of the skin, oral mucosa, eyes, and liver 5 months after myeloablative HLA-matched alloHSCT for acute myeloid leukemia in first complete remission and GVHD prophylaxis with CsA and MMF but fails to show improvement of symptoms. Which treatment modality would be your next choice?

In the 2009 survey 13 centers added a CNI (11 CsA and 2 tacrolimus), 4 added ECP, and 2 applied a pulse of CS or MMF, respectively. One center would have added an mTORi and another azathioprine after a pulse of CS. Several centers suggested using a triple-agent combination consisting of CsA, a pulse of CS, and ECP (n = 1); CS, CsA, and MMF (n = 1), CNI combined with methotrexate or sirolimus; and ECP (n = 1), CS, CsA, and ECP (n = 4). One center suggested adding 3 agents to CS consisting of CsA, ECP, and rituximab. One center listed several treatment options, including MMF, sirolimus, pulse of CS, methotrexate, alemtuzumab, etanercept, or rituximab.

In contrast to the 2009 survey the current analysis revealed the following results: 14 centers would add ECP only, 1 ECP and sirolimus, 4 CsA, and 3 RUX. Other treatment options reported by single centers were to add EV or MMF or combine sirolimus and RUX or consider a short course of high-dose CS. In addition, other single centers suggested a short course of high-dose CS in combination with ECP and pentostatine or tacrolimus.

The next question of the 2009 survey was whether mTORi was combined with CNI in second-line treatment of cGVHD. Seventeen centers stated avoiding completely the combination of mTORi and CNIs. Fourteen centers applied the combination of tacrolimus and mTORi (7 EV and 7 sirolimus). Ten centers combined CsA with mTORi (5 EV and 5 sirolimus).

In addition, the combination partners of ECP in second-line treatment were requested. Twenty-three centers combined ECP with CS and a CNI, 16 with CS, 10 with CS and an mTORi, 2 with a CNI without additional CS, 14 with MMF and CS, and 2 with CS, a CNI, and MMF. One center used ECP as single-agent treatment or combined ECP with CS, a CNI, or an mTORi, respectively. The centers in Switzerland did not use ECP at all in 2009 because of a lack of reimbursement.

How do you treat in the second line a patient with severe cGVHD with deep cutaneous sclerosis, moderate ocular and oral involvement, with normal platelet counts? Please provide also ranking according to treatment lines.

The results are shown in Figure 4, and the ranking is depicted in the Supplementary Appendix. In addition, within the 2009 survey etanercept, azathioprine, basiliximab, alemtuzumab, and hydroxychloroquine were reported by single centers only, whereas within the 2018 survey tocilizumab and mesenchymal stromal cells were reported by 2 centers for the first time and

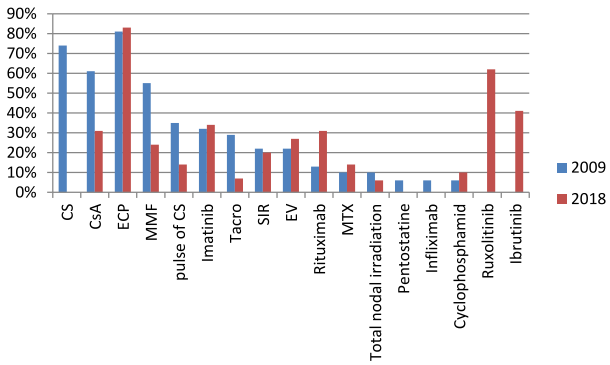

Figure 4. Applied salvage treatment for cGVHD with cutaneous deep sclerosis. CS was not included in the 2018 survey as a treatment option.

pomalidomide, bortezomib, azathioprine, and regulatory T cells were reported by single centers in advanced lines only.

A patient with primary treatment consisting of CS and CsA for quiescent onset cGVHD with moderate skin, oral, and liver involvement after alloHSCT for standard-risk acute myeloid leukemia in first complete remission shows complete response of the skin and liver manifestations but lacks improvement of oral manifestations. What would be your next step?

Twenty-eight centers (90%) would not change systemic immunosuppression and would add topical budesonide (n = 8), topical tacrolimus (n = 11), topical CS not specified (n = 10), or topical dexamethasone (n = 3). Four other centers would add a variety of topical steroids, and 5 centers would add topical CsA. Three centers would change systemic immunosuppression, adding MMF (n = 1) or ECP (n = 2), but would apply in addition topical treatment with either tacrolimus (n = 1) or topical CS (n = 2). Only 1 center would not use topical immunosuppression and would start EV to improve oral cGVHD. The last question was part of the 2009 survey only.

DISCUSSION

cGVHD remains the most relevant cause for late morbidity and mortality [1,3] and together with acute GVHD represents the major limiting factor for broader application of alloHSCT. This survey documents the variability in treatment of cGVHD because of the limited evidence currently available for the clinical community [8,17,18]. Overall, first-line treatment of cGVHD is applied relatively homogeneously, and the 2018 survey showed even decreased variability with the exception of a tendency of decreased use of CNI. The latter can be explained by limited data on the role of CNI in standard-risk cGVHD after alloHSCT because the standard defining randomized trial was performed in recipients after sibling bone marrow transplantation, with myeloablative conditioning failing to show a major impact of CNI on response and survival [9]. Interestingly, low platelets at diagnosis of cGVHD are still considered as a high-risk feature because more centers apply a combination of CS and CNI compared with a "normal platelet" scenario [10]. Overall, the results are in line with a survey and guidelines provided by the European Society for Blood and Marrow Transplantation for treatment of cGVHD [22,23] and by a recent survey by the Italian transplant group [24] and a review by Martin et al. [8] indicating a broad consensus on the initial treatment of cGVHD.

An area of uncertainty remains the speed of taper of CS after response to cGVHD as documented by the 2009 survey, which is in line with results from a recent survey from the Italian transplant group and is most likely due to lack of controlled trials comparing different CS taper schedules in cGVHD [24]. The same applies to the various target drug levels of mTORi and CNI that have been studied in acute GVHD but to a lesser extend in cGVHD. Moreover, patients with cGVHD are more prone to comorbidities potentially interfering with the application of higher drug doses like vascular and renal toxicity [25].

The significant variation treating patients with progressive onset type of cGVHD can be explained by the fact that onset of this form of cGVHD frequently occurs during treatment of acute GVHD with CS [26], and existing evidence has repeatedly confirmed the inferior prognosis of progressive onset type [3,27]. Both surveys document ECP as the leading treatment option in progressive onset type of cGVHD, most likely because infectious mortality is the leading cause of death in the latter population and ECP is known not to cause generalized immunosuppression and does not increase infectious risks [28,29]. However, trials evaluating ECP specifically in progressive onset type of cGVHD are lacking.

In addition, the surveys also confirm a significant heterogeneity in treatment of BOS which may be due to the lack of BOS-specific trials [19]. Surprisingly, even BOS-specific treatment differed considerably, and only 13 of 29 centers applied the complete fomoterol, azithromycin and montelukast (FAM) regimen despite a published trial [20]. Moreover, 1 center reported to have stopped using azithromycin due to the FDA warning on increased risk for relapse [21], although the latter applied to prophylaxis in the absence of cGVHD and not treatment of manifest BOS. Of note, ECP was reported as the leading systemic treatment option in BOS most likely based on the low risk for additional infectious morbidity and mortality and reviews on the topic and efficacy in treatment of BO after lung transplantation [30-32].

Both surveys document major variations in practice in second-line treatment that has been already shown by a survey of the Italian transplant group [24], with ECP being the most frequently applied treatment option. Moreover, the 2018 survey also demonstrates that new treatment options like ibrutinib [33] are used after failure of first-line treatment, and even published retrospective analyses influence clinical practice as documented by the increasing use of RUX in the treatment of cGVHD [34]. Moreover, evidence may drive clinical decisions as documented by the declining use of MMF in treatment of cGVHD most likely explained by the lack of efficacy in first-line treatment [35].

The surveys have 3 limitations. First, although a significant percentage of transplant activities were captured in both surveys, it is likely that practice in nonparticipating centers is more heterogeneous because centers actively participating in the activities of the German-Austrian-Swiss GVHD Consortium responded to a significantly higher percentage and may share more clinical interest in cGVHD compared with nonresponding centers, taking into account that response rates did not correlate with center size. An additional limitation is the selection of questions with predefined options. Therefore, only part of the clinical practice was captured, and although comments or additional options were permitted, the predefined answer options may have caused bias of the responding centers. Third, responding persons and centers had a significant overlap between both surveys but were not identical, preventing a statistical conclusion. Therefore, the results remain descriptive.

In summary, the surveys underline the critical need for prospective trials evaluating the role of CNI in first-line treatment as well as prospective trials in second-line treatment [36]. Moreover, steroid-dependent and -refractory cGVHD is still

treated with a "trial and error" approach as demonstrated by a significant variety of practice because of the lack of a biomarker or disease pattern predicting response to a specific drug, which is most likely due to a broader variability of the underlying pathophysiology [37,38]. Therefore, any future trial should be accompanied with an assessment of biomarkers potentially predicting response at onset of treatment [39].

ACKNOWLEDGMENTS

The authors acknowledge the work of S. Gleich, who collected the data, as well as all participating centers. Moreover, A. Hackl supported the analysis in 2009.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: D.W. received honoraria from Novartis, Mallinckrodt, and Neovii. H.G. received honoraria for presentations at scientific meetings from Mallinckrodt, Novartis, Amgen, and Cellgene. R.Z. received honoraria from Novartis, Mallinckrodt, and Incyte. E.W.-D. received travel support from Medac and honoraria from Novartis. E.H. received honoraria from Novartis.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.03.003.

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