Transplantation and Cellular Therapy 31 (2025) 450.e1–450.e10

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Allogeneic – Adult

Changes in Chronic Graft-versus-Host Disease Treatment Over Time: A 15-Years Survey Within Allogeneic Hematopoietic Stem Cell Transplant Centers in Germany, Austria, and Switzerland

Alexander Denk[1,*], Matthias Alexander Fante[1], Silke Heidenreich[2], Hildegard T. Greinix[3], Eva-Maria Wagner Drouet[4], Katharina Egger-Heidrich[5], Julia Marx[6], Darina Kodzhabasheva[7], William Krüger[8], Gesine Bug[9], Claudia Wehr[10], Joerg Halter[11], Irene Teichert von Lüttichau[12], Lutz Peter Mueller[13], Olaf Penack[14], Inken Hilgendorf[15], Guido Kobbe[16], Stefan Klein[17], Anita Lawitschka[18], Jochen Frietsch[19], Julia Winkler[20], Daniel Wolff[1]

[1] *Internal Medicine III - Hematology and Oncology, University Hospital Regensburg, Regensburg, Germany*
[2] *Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[3] *Division of Hematology, Medical University of Graz, Graz, Austria*
[4] *Department of Internal Medicine III, Johannes Gutenberg-University Mainz, Mainz, Germany, Mainz, Germany*
[5] *Department of Internal Medicine 1, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany*
[6] *Department of Medicine A (Hematology, Hemostaseology, Oncology, Pneumology), University Hospital Muenster, Muenster, Germany*
[7] *Department of Internal Medicine II, St. Johannes Hospital Dortmund, Dortmund, Germany*
[8] *Klinik für Innere Medizin C - Hämatologie, Onkologie, Stammzelltransplantation, Palliativmedizin, Universitätsmedizin Greifswald, Greifswald, Germany*
[9] *Department for Hematology and Oncology, University Hospital Frankfurt, Frankfurt, Germany*
[10] *Department of Hematology, Oncology and Stem Cell Transplantation, Faculty of Medicine, University of Freiburg, Freiburg, Germany*
[11] *Department of Hematology, University Hospital Basel, Basel, Switzerland*
[12] *Department Clinical Medicine, Zentrum für Kinder und Jugendmedizin, TUM School of Medicine and Health, München, Germany*
[13] *Department of Internal Medicine IV, University Hospital Halle, Halle, Germany*
[14] *Department of Hematology, Oncology and Tumorimmunology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany*
[15] *Department of Internal Medicine, Hematology and Oncology, University Hospital Jena, Germany*
[16] *Department of Hematology, Oncology and Clinical Immunology, University Hospital Duesseldorf, Duesseldorf, Germany*
[17] *Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany*
[18] *Department of Pediatrics, St. Anna Children's Hospital, Medical University of Vienna, Vienna, Austria*
[19] *Department of Internal Medicine II, University Hospital Wuerzburg, Wuerzburg, Germany*
[20] *Department of Internal Medicine 5, Hematology/Oncology, University Hospital Erlangen, Erlangen, Germany*

Article history:
Received 8 December 2024
Accepted 26 April 2025

A B S T R A C T

Background: Chronic graft-versus-host disease (cGVHD) represents a major complication after allogeneic stem cell transplantation (alloHSCT). In 2009 and 2018 a survey among German, Austrian, and Swiss transplant centers showed a homogeneous 1st-line

Financial disclosure: See Acknowledgments on page 450.e8.

*Correspondence and reprint requests: Alexander Denk, MD, Department of Internal Medicine III, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg, 93053 Germany.
E-mail address: alexander.denk@ukr.de (A. Denk).

https://doi.org/10.1016/j.jtct.2025.04.017

Key Word:
Allogeneic hematopoietic stem cell transplantation
Bone marrow transplantation
Chronic graft-versus-host disease
Immunosuppressive therapy
Steroids
Ruxolitinib
Belumosudil

treatment practice, while 2nd-line treatment as well as management of progressive onset type and bronchiolitis obliterans syndrome (BOS) displayed significant heterogeneity. Since the last survey, ruxolitinib (rux) has been approved and other new agents are explored in treatment of cGVHD.

Objective: We conducted a follow-up survey in 2024 to document the impact of recent approvals and new agents on treatment pattern focusing on management of 2nd-line treatment, progressive onset type, BOS, and sclerotic manifestations.

Study design: A paper-and-pencil-based questionnaire was sent electronically to 60 German speaking centers performing alloHSCT. 20 centers responded, representing 45% of the patients receiving an alloHSCT in 2023 in Germany, Austria, and Switzerland.

Results: In 1st-line treatment of classic standard risk cGVHD, single agent prednisone represents standard of care (14/20 centers) which may be combined with calcineurin inhibitor (CNI) (4/20), while rux is used in selected cases only. In 2nd-line treatment rux is now used by the majority of centers (19/20). In the presence of cytopenia, rux remains the preferred agent (12/20) while use of extracorporeal photopheresis (ECP) is considered by 8 of 20 centers. In case of active infections, ECP is preferred by 15 of 20 centers and both agents are regarded as steroid-sparing agents in 2nd-line treatment of steroid-dependent cGVHD. Rux would be applied in the presence of active infections by 5/20 centers only. Moreover, rux (15/20) and ECP (6/20) are also preferred treatment modalities in treatment of progressive onset cGVHD. For BOS, systemic and inhalative corticosteroids, montelukast and azithromycin (FAM, 13/20), rux (15/20), ECP (17/20) and CNI (10/20) are frequently applied agents, while abatacept (8/20), belumosudil (7/20), imatinib (5/20), mycophenolate mofetil (MMF) (5/20), everolimus (4/20) and ibrutinib (3/20) are used as salvage options in selected patients only. In case of new sclerotic manifestations after failure of 2nd-line treatment including steroids, CNI and rux, most centers would use ECP (14/20), whereas subsequent or alternative salvage treatment of sclerotic manifestations remains heterogenous comprising belumosudil (13/20), ibrutinib (5/20), imatinib (5/20), rituximab (4/20), cyclosporine (3/20), tacrolimus (3/20), everolimus (3/20), sirolimus (3/20), methotrexate (3/20) and MMF (3/20). The preferred taper sequence of immunosuppressive agents in case of response applied in 12/20 centers is initial taper of steroids, followed by taper of CNI and final termination of rux.

Conclusion: The survey documents the effect of evidence and approval on clinical care with single agent prednisone representing the standard of care in 1st-line treatment while rux combined with steroids defines the new standard for 2nd-line treatment of cGVHD. ECP is used in case of contraindication for rux and both agents are also used in progressive onset cGVHD. In contrast, treatment of BOS and sclerotic cGVHD beyond 2nd-line treatment remains heterogeneous with new agents being integrated in the treatment landscape.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) represents a major complication after allogeneic stem cell transplantation (alloHSCT) that significantly contributes to nonrelapse mortality (NRM) and reduced quality of life [1,2]. The National Institutes of Health proposed consensus guidelines for diagnosis and severity grading of GVHD within clinical trials [3–5], which have been included in clinical routine [6]. In contrast to the guidelines for diagnosis and staging of GVHD, detailed guidelines for treatment of cGVHD are lacking, which is mainly due to the lack of controlled trials in salvage treatment and lack of controlled trials in 1st-line treatment showing a superior outcome for combination therapies [7]. To document treatment pattern and assess the impact of emerging new treatment options in cGVHD, a survey among German, Austrian, and Swiss transplant centers was first performed in 2009 and repeated in 2018 that covered specific treatment decisions on first- and second-line treatment of cGVHD as well as an assessment of all potential treatments applied in clinical care of cGVHD [8].

Since the last survey, several new agents have been explored in clinical studies for treatment of cGVHD [9–16]. Ibrutinib was the first agent to be approved by the United States Food and Drug Administration (FDA) for 2nd-line treatment in

2017 [17], and has been used in Germany occasionally off-label since its initial approval in the US. In 2021, ruxolitinib (rux) was also approved by the FDA and one year later by the European Medicines Agency (EMA) for 2nd-line treatment [18,19]. Recently, other agents like belumosodil and axatilimab have been explored in the treatment of cGVHD resulting in FDA approval [20,21], while belumosudil can only be applied by a case by case application at the insurance due to the lack of approval by the EMA. In addition, a European Society for Blood and Marrow Transplantation (EBMT) & Center for International Blood and Marrow Transplant Research (CIBMTR) taskforce published joint guidelines for definition of steroid-dependent and steroid-resistant cGVHD [22].

Therefore, we conducted a new survey to document the impact of new approvals, agents, and guidelines on treatment pattern focusing on management of 2nd-line treatment, progressive onset type, bronchiolitis obliterans syndrome (BOS), and sclerotic manifestations of cGVHD.

METHODS

A paper-and-pencil-based questionnaire on current clinical practice of first-line, second-line, and management of progressive onset type, BOS and sclerotic manifestations of cGVHD was sent electronically to the principal investigators of 60 centers performing alloHSCT within Germany, Austria, and Switzerland. Twenty centers responded, representing 45% of German, 32% of Austrian, and 62% of Swiss (only German-speaking centers included) transplant activities. The participating centers are listed in the Supplementary Appendix (S1).

In summary, of the 20 centers responding to the 2024 survey, 17 had responded to the 2018 survey, while two centers participated for the first time in the survey. Total 14/20 centers already answered in 2009 to the survey [8].

In the current survey, five questions (questions 1, 6a, 6b, 10a, 10b) referred to 1st-line therapy, of which two were also asked in the previous surveys. Six questions (questions 2a-c, 3, 4, 5) referred to 2nd-line therapy, of which all six questions were posed for the first time. Three questions (questions 7, 8, 9) targeted progressive onset GVHD, of which two had already been asked in the two previous surveys. One question (question 11) targeted BOS, and this question was also asked in the previous surveys. Two questions (questions 12, 14) referred to sclerosing manifestations, of which one question was also asked in a previous survey. One new question targeted the tapering sequence of immunosuppressive agents. The original questionnaires of 2024, 2018 and 2009 are provided in the Supplementary Appendix (S2). Additionally, every single question in all three questionnaires is provided with a reference to whether and in which questionnaires the respective question was asked again or not.

RESULTS

First-Line Treatment

In the first question of the survey, the approach to 1st-line treatment of classic standard risk cGVHD was asked. In line with the two previous surveys, single agent prednisone remains the standard of care (14/20 centers) in 2024, which may be combined with calcineurin inhibitor (CNI) (4/20). One center would add rux and topical therapy to prednisone, while one center opted for solely topical therapy. The results of question 1 are depicted in Figure 1.

We also asked for a complete list of potential treatment options applied in 1st-line treatment of classic cGVHD excluding progressive onset (question 6a). Of note, in 2018 rux was reported for the first time by one center as potential option in 1st-line treatment and nine centers continued using corticosteroids (CS) and CNI only. In 2024, five centers opted for rux as a potential option in 1st-line treatment. Eleven centers would still continue using CS and CNI only. The results of question 6a are shown in Figure 2.

We also asked whether the respective transplant centers occasionally use steroid-free systemic immunosuppression for initial treatment of moderate cGVHD (question 6b). While 12 centers denied using steroid-free systemic immunosuppression for moderate cGVHD, one center stated to use steroid-free systemic immunosuppression only in very rare occasions. In contrast, seven centers use steroid-free systemic immunosuppression with rux (single agent or in combination with other immunosuppressants) being the most frequent agent used (6 of 7 centers), while one center used CNI mono. Extracorporeal photopheresis (ECP) (n = 4), sirolimus (n = 1), mycophenolate mofetil (MMF) (n = 1) and mTOR-inhibitor (mTORi) (n = 1) were considered options in combination with rux.

Questions 10a and 10b focused on the use of rux in 1st-line treatment of cGVHD.

Question 10a asked for agents combined with rux in 1st-line treatment. Nine centers stated not using rux in 1st-line treatment, while one center stated using rux only in very rare cases. If rux was used, one center applied rux as single-agent

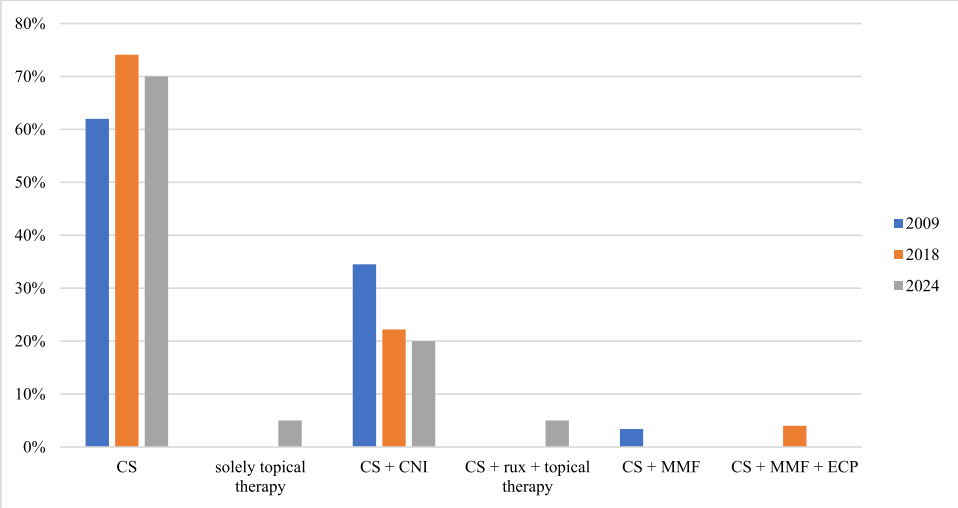

Figure 1. 1st-line treatment of moderate cGVHD with normal platelets. CS = corticosteroids, ECP = extracorporeal photopheresis, MMF = mycophenolate mofetil.

treatment and nine centers combined it with CS. Other, but less frequently chosen agents for combination with rux are depicted in the Supplementary Appendix (S3).

Question 10b asked for the scenario in which rux is considered in 1st-line treatment or at least in which scenario it could be imagined so. The most frequent reasons for use of rux in 1st-line treatment were (in descending order): (i) Progressive onset cGVHD (n = 8), (ii) anticipated relevant side effects to CS (n = 6), and (iii) to taper CS (n = 3). A more detailed list of all options chosen is depicted in (S3).

Second-Line Treatment

The next questions dealt with second-line treatment of cGVHD:

Question 2a depicted a scenario of a patient suffering from steroid-refractory cGVHD requiring 2nd-line treatment. In this case, the majority (15/20 centers) would add rux to CS without increasing the dose of the latter. Other options chosen are listed in (S3). In total, 19 centers considered use of rux for 2nd-line treatment.

The next two questions (question 2b and 2c) asked for the impact of cytopenia and infectious history:

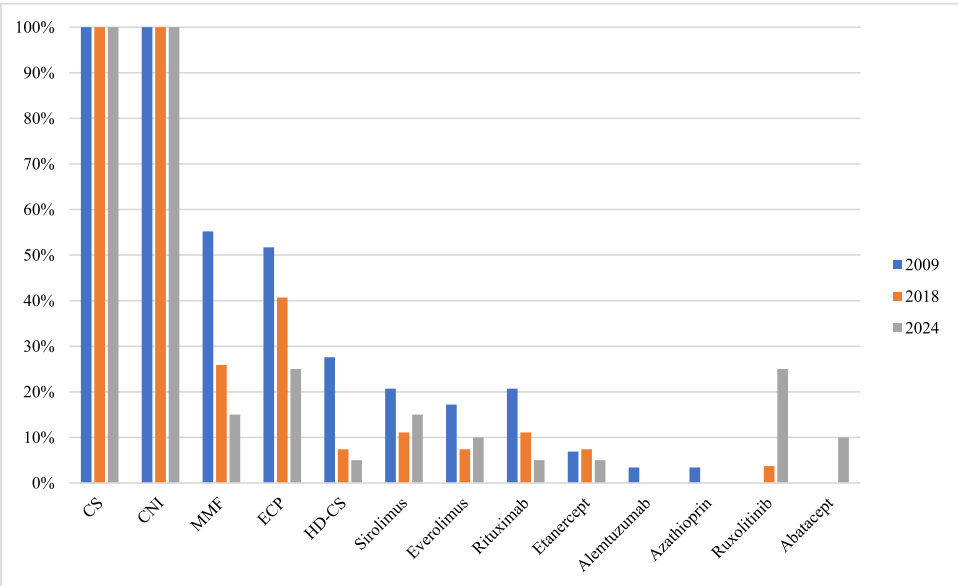

Figure 2. Applied 1st-line treatments in classic cGVHD without progressive onset. ECP = extracorporeal photopheresis, HD-CS = high-dose CS, MMF = mycophenolate mofetil.

In case of cytopenia (question 2b), most centers (n = 9) would opt for prednisone 0.5 mg/kg/d plus rux, while second most centers (n = 4) would choose a combination of prednisone 0.5 mg/kg/d plus ECP. Less frequently chosen options are listed in (S3). Taken together, in case of cytopenia 12/20 centers considered use of rux and 8/20 centers considered use of ECP for 2nd-line therapy, respectively.

In case of cytopenia and prior infectious complications (question 2c), only 4/20 of the centers would opt for prednisone 0.5 mg/kg/d in combination with rux, and one center for prednisone 0.25 mg/kg/d combined with rux. Eight centers would choose a combination of prednisone 0.5 mg/kg/d plus ECP, while one center would use a pulse of prednisone 1.0 mg/kg/d in combination with ECP and intravenous immunoglobulins. A list of all answers given can be found in (S3).

Questions 3 dealt with failure of 2nd-line treatment, while question 4 targeted steroid-dependency in 1st-line treatment:

In case of a patient suffering from steroid- and rux-refractory cGVHD and thrombocytopenia (question 3), most centers (n = 16) would continue the ongoing therapy and add ECP. A list of all answers given can be found in (S3).

Depicting a scenario of a patient with steroid-dependent cGVHD (question 4), the majority (15 centers) would add rux, and two of these centers would additionally increase the steroid dose. A full list of answers given is provided in (S3).

In the presence of prior and current infectious complications in a patient with steroid-dependent cGVHD (question 5), the majority of participating centers (n = 11) would add ECP to CS (prednisone 0.5 mg/kg/d) for 2nd-line treatment, while four centers considered a combination with rux. Less frequently chosen options are listed in (S3). Taken together, ECP was considered by 15 centers, while rux was considered by five centers.

The next two questions focused on progressive onset of cGVHD:

Question 7 depicted a patient with progressive onset of cGVHD during treatment of acute GVHD of the skin and gut (both in remission) during taper of steroids on a dose of prednisone 0.5 mg/kg/day and CNI with moderate involvement of the skin, oral mucosa, and liver and platelets of 55/nl.

Regarding the next treatment strategy, in the 2009 and 2018 surveys most centers stated to increase the CS dose, continue CNI, and start a new agent with ECP, MMF or (in the 2018 survey) rux being the most frequent ones. In both surveys, as the second most frequently mentioned option most centers would have increased the CS dose only, respectively [8].

In the 2024 survey, most centers (n = 7) still would increase the CS dose, continue CNI, and start a new agent (rux [n = 3], ECP [n = 2], rux with or without ECP and with or without MMF [n = 1], rux or ECP [n = 1]). Six centers continued CS and CNI at the same dose with all of them adding rux. Less frequently chosen options are listed in (S3). In total, rux was considered by 15 centers, while ECP was considered by six centers.

Question 8 repeated the prior case of progressive onset, except that the patient was additionally on treatment with rux when cGVHD started. In the 2024 survey, four centers stated to increase the CS dose, continue CNI and rux, and start a new agent (ECP [n = 2], ECP with or without MMF [n = 1], or either ECP or MMF or methotrexate (MTX) [n = 1]). Another four centers increased CS, continued CNI but stopped rux and started ECP instead. Another four centers increased CS, continued rux but stopped CNI and started ECP instead. Less frequently chosen options are depicted in (S3).

Question 9 referred to a patient with steroid-refractory acute GVHD (aGVHD) who developed cGVHD in addition to preexisting aGVHD.

In the 2024 survey the majority of centers (n = 12, 60%) stated to continue CS and CNI at the same dose with ten of them adding rux, one center adding rux or ECP and one center adding ECP. Four centers continued CS but terminated CNI with three of them adding rux and one center adding rux, ECP and topical therapy instead. A complete list of options chosen can be found in (S3).

In contrast, in the 2009 survey most centers (n = 13, 42%) stated using an increased dose of CS, continuing CNI, and starting either MMF or ECP in this case. Each nine centers (29%) would have either increased the CS dose as the only therapeutic intervention and would have continued CNI or would have continued CNI and CS at the same dose adding another agent with MMF and ECP being preferred options. The 2018 survey revealed no major differences to the prior approach except increasing the use of ECP and declining the use of MMF, with four centers (14%) increasing the CS dose only.

The next question (question 11) evaluated the organ-specific approach in the treatment of 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 (S4).

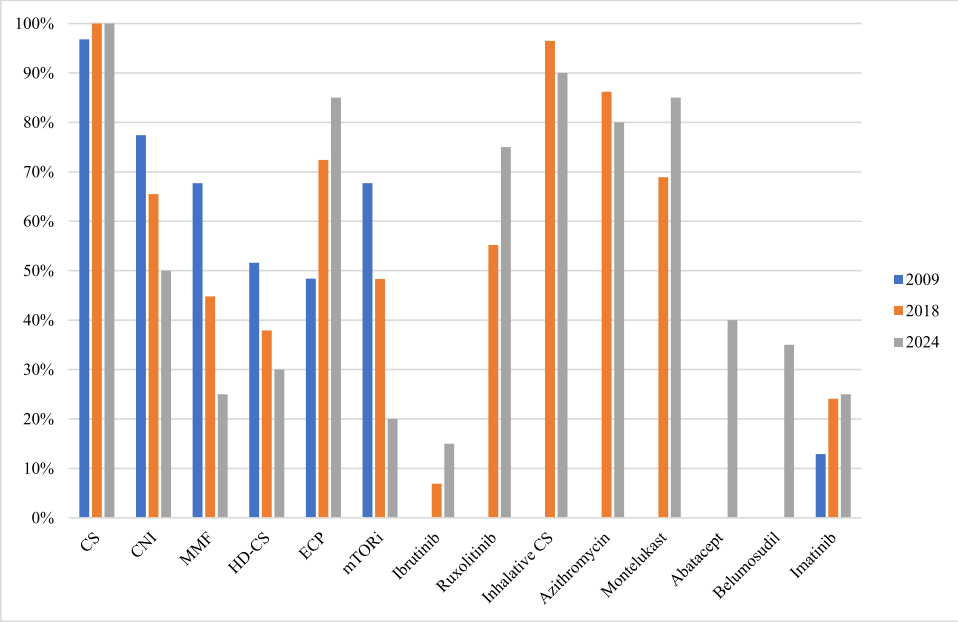

Figure 3. Most frequently applied systemic treatments of BOS comparing 2024 with 2018 and 2009.

Generally, in 2024, trends from 2018 (compared to the 2009 survey) continued. CS was still the most important treatment option; the increasing use of ECP continued (17/20), while only 5 of 20 centers still used MMF. Azithromycin was used by 16 of 20 centers, montelukast was used by 17 of 20 centers with 11 centers using inhalative steroids (fluticasone), azithromycin and montelukast (FAM-regimen) upfront [23]. One center used FAM-regimen from 2nd-line onwards and one center did not specify in which therapeutic line the FAM-regimen was used. Again, rux entered the field in treatment of BOS (n = 15). Imatinib (5/20), everolimus (4/20) and ibrutinib (3/20) were used in selected cases only. Moreover, abatacept (n = 8) and belumosudil (n = 7) became treatment options for BOS since the last survey; one additional center stated that both abatacept and belumosudil represent potential treatment options for BOS without having applied these two agents, so far. The results of question 11 are shown in Figure 3.

Question 13 targeted the taper of immunosuppression in 2nd-line treatment of cGVHD:

The preferred taper sequence of immunosuppressive agents in case of response applied in 12/20 centers is primary taper of steroids, followed by taper of CNI and final termination of rux. Four centers preferred reduction of CS, followed by termination of CNI, then by termination of rux and then by final taper of CS. Less frequently chosen options are listed in (S3).

Questions 12 and 14 focused on sclerosing manifestations of cGVHD:

Question 12 depicted a patient with increasing deep sclerosis of the skin despite ongoing treatment with prednisone, cyclosporine (CsA) and rux asking for the next preferred therapeutic option:

In skin sclerosis, 16 different combinations were reported, which are listed in (S3). In total, ECP was the most frequently applied strategy (n = 14), followed by rux (n = 12), CS (n = 9) CNI (n = 8), and belumosudil (n = 5). In total, eight centers opted for a steroid-free approach.

The last question (question 14) evaluated the approach in 2nd-line treatment of steroid-refractory sclerosing cGVHD:

The results are shown in Figure 4, and the ranking is depicted in the Supplementary Appendix (S4). In the 2024 survey, rux (19/20) and ECP (17/20) are preferred treatment options next to CS (7/20) and CNI (tacrolimus n = 3, CsA n = 3). Belumosudil is now considered as a relevant treatment option (n = 13), while FDA-approved ibrutinib was used by five centers.

DISCUSSION

Although cGVHD remains the most relevant cause for late morbidity and mortality [24,25] after alloHSCT, initial treatment continues to fail in approximately half of patients and subsequent treatment lines are applied with a trial and error approach. The 2018 and 2009 surveys demonstrated that 1st-line treatment of cGVHD is applied

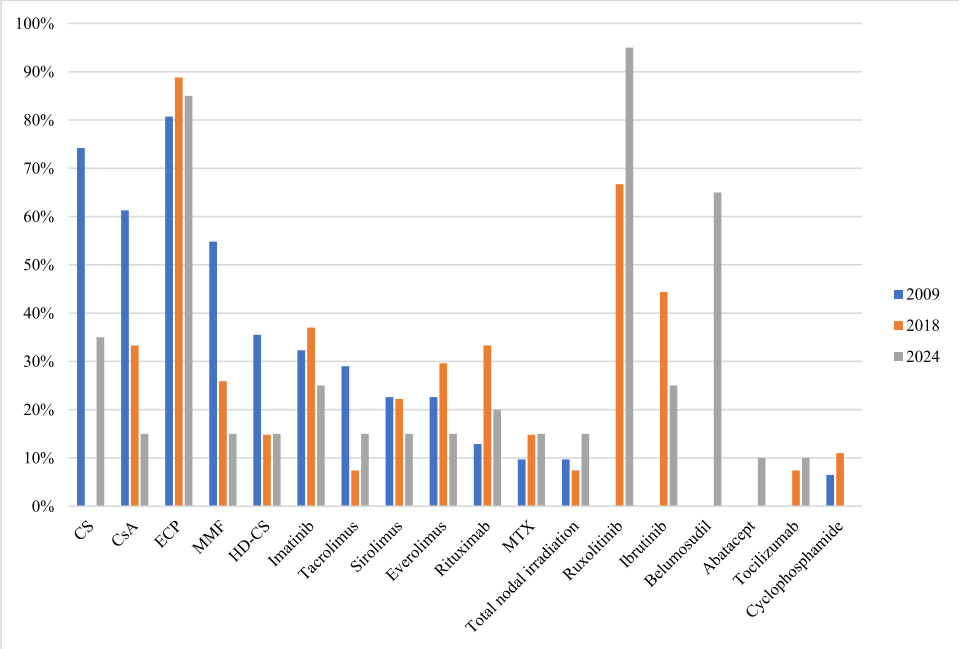

Figure 4. Applied salvage treatment for cGVHD with cutaneous deep sclerosis. CS were not included in the 2018 survey as a treatment option.

relatively homogeneously [8], which is in line with guidelines provided by the EBMT for treatment of cGVHD [26–28] and a survey by the Italian transplant group [29] indicating a broad consensus on the initial treatment of cGVHD. The current survey shows that single agent CS still represents standard of care which may be combined with a CNI, while rux or ECP are used in selected cases only.

Steroid-refractory cGVHD continues to pose a therapeutic challenge for patients due to the fact that empiric 2nd line treatments show unsatisfactory outcomes [30–33]. Based on the REACH3 trial, rux has been approved for 2nd-line treatment of cGVHD [10]. In consequence, rux is now mostly used while ECP is applied in patients with cytopenia especially in steroid-dependent cGvHD. In case of infections, ECP continues to be the preferred strategy due an increased risk of cytopenia and infectious complications associated with rux [10,34].

Both agents are regarded as steroid-sparing in 2nd-line treatment of steroid-dependent cGVHD which is in line with published data [10,35–37].

In line with the previous survey, there is still significant variation in treatment approaches in progressive onset type of cGVHD [8]. While in the past survey ECP has been shown to be the leading treatment option in progressive onset type of cGVHD, most likely because ECP does not increase infectious risks [37,38], the updated survey displayed ECP use behind rux as preferred treatment modality based on the fact that rux has been approved and thus, most centers have access to it.

In addition, the updated survey confirms a significant heterogeneity in treatment of BOS as BOS-specific trials are mostly lacking. The use of rux was described in BOS [39], and one trial recently confirmed efficacy in pulmonary cGVHD [40]. Next to rux, systemic and inhalative CS, ECP, CNI and additional montelukast in combination with azithromycin are preferred agents, while abatacept and belumosudil are used as salvage treatment in selected patients [41,42].

In case of new cutaneous sclerosis after failure of CS, CNI and rux, over 80% of centers would use ECP, but salvage treatment of sclerotic manifestations remains heterogenous with belumosudil (13/20) ibrutinib (5/20), and imatinib being the most frequent options applied.

Belumosudil is generally considered effective in treatment of cGVHD but remains to be used in selected patients only most likely due to the lack of EMA approval and access to this agent.

The preferred sequence in tapering immunosuppressive agents after response to treatment is primarily taper of steroids, followed by taper of CNI and final taper of rux most likely driven by the toxicity profile and prior failure of the applied agents.

While our survey documents that 2nd-line treatment has become more homogenous with rux and ECP being the most important agents, there are ongoing major variations in practice in

progressive onset type, BOS and sclerosing manifestations of cGVHD. The latter fact might be a result of published prospective analyses influencing clinical practice in these fields as documented by the increasing use of abatacept or belumosudil in the treatment of cGVHD [14,15,20].

Based on promising results in 2nd-line treatment, rux is also being occasionally applied in 1st-line in selected situations as our survey demonstrates.

The survey has 4 limitations. First, although a significant percentage of transplant activities were captured, 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 the three surveys but were not identical, preventing a statistically valid conclusion. Therefore, the results remain descriptive. Fourth, the questionary was sent to the principal investigators to ensure that the answers provided reflect the standard of the respective centers. However, individual bias of the investigators answering the questionnaire cannot be excluded.

In this manuscript we focused on inclusion of certain clinical vignettes (1st-line therapy, 2nd-line, progressive onset GVHD, sclerosing manifestations, BOS, and variations considering cytopenia or serious infections) in order to present a) standard situations of daily practice (1st-line treatment, 2nd-line treatment with or without usage of rux) and b) difficult situations of certain expected heterogeneity (BOS, sclerotic manifestations, progressive onset cGVHD) to detect impact of new treatment options. Therefore, we did not focus on 3rd-, or 4th-line therapies.

In summary, rux defines the new standard in 2nd-line treatment of cGVHD defines. ECP is used in case of contraindication for rux and both agents are also used in progressive cGVHD. In contrast, BOS and cutaneous sclerosis are treated relatively heterogeneously after failure of 1st-line treatment. Multicenter randomized clinical trials for first-, second-, and advanced-line cGVHD remain mandatory to optimize and harmonize cGVHD. Moreover, the ongoing trial & error approach leads to prolonged treatment calling for a joint effort towards a biology driven approach applying predictive biomarker.

ACKNOWLEDGMENTS

The authors acknowledge the work of all participating centers.

Financial disclosure: None.

Conflict of Interest Statement: D.W. has received research funds from Novartis and honoraria from Novartis, Mallinckrodt, Incyte, Sanofi, Behring, Takeda, and Gilead. M.A.F. has received honoraria from Novartis and Sanofi and travel support from Sanofi. H.T.G. received honoraria and speakers bureau from Therakos, Novartis, Stemline and Sanofi, speakers bureau from Gilead and honoraria from Neovii and BMS. E.-M.W.D. holds membership on an entity's Board of Directors or advisory committees from Novartis, Kite, Takeda and Incyte, received honoraria from Kite and Takeda and travel support from Takeda and BMS. G.B. received honoraria from BMS, Gilead, Jazz and Novartis and travel grant from Gilead and Jazz. C.W. received honoraria and travel grant from Takeda, MSD and Jazz. L.P.M holds membership on an entity's Board of Directors or advisory committees from Pfizer, Gilead, Novartis and Amgen, received research funding from Amgen, received honoraria from Abbvie, BMS and Squibb and travel grant from Gilead, Abbvie, BMS and Squibb. O.P. holds membership on an entity's Board of Directors or advisory committees from Apogepha, Equilium, Bio, Omeros, Orca Bio, Priothera, Sanofi, Shionogi and SOBI, received honoraria and travel grant from Alexion, Gilead, Jazz, MSD and Novartis, travel grant from Pfizer and Mallinckrodt and research funding from Incyte and Priothera. I.H. received honoraria from Abbvie, medac, Novartis and Takeda. G.K. received honoraria and research funding from MSD, Amgen, Abbvie and medac, honoraria from Pfizer, Novartis, Gilead, BMS, Biotest, Takeda, Eurocept and Jazz and research funding from Eurocept. A.L. received honoraria from Novartis, Takeda and medac. J.F. received honoraria from Jansen and Novartis. All other authors have no competing interests.

Authorship statement: Alexander Denk: data collection, analysis of the data, writing of the manuscript. Matthias Alexander Fante, Silke Heidenreich, Hildegard T. Greinix, Eva-Maria Wagner Drouet, Katharina Egger-Heidrich, Julia Marx,

Darina Kodzhabasheva, William Krüger, Gesine Bug, Claudia Wehr, Joerg Halter, Irene Teichert von Lüttichau, Lutz Peter Mueller, Olaf Penack, Inken Hilgendorf, Guido Kobbe, Stefan Klein, Anita Lawitschka, Jochen Frietsch and Julia Winkler: treatment of patients, correction of manuscript. Daniel Wolff: study and survey conception, supervision of the project, data collection, correction of manuscript. Data Availability: All data that support the findings of this study are included in the manuscript and supplementary material. Category of manuscript: Regular manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2025.04.017.

REFERENCES

1. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2006;108(8):2867–2873. https://doi.org/10.1182/blood-2006-02-003954.
2. Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood*. 2011;117(17):4651–4657. https://doi.org/10.1182/blood-2010-11-319509.
3. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transpl*. 2015;21(3):389–401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001.
4. Martin PJ, Lee SJ, Przepiorka D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. The 2014 Clinical Trial Design Working Group Report. *Biol Blood Marrow Transpl*. 2015;21(8):1343–1359. https://doi.org/10.1016/j.bbmt.2015.05.004.
5. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transpl*. 2015;21(6):984–999. https://doi.org/10.1016/j.bbmt.2015.02.025.
6. Duarte RF, Greinix H, Rabin B, et al. Uptake and use of recommendations for the diagnosis, severity scoring and management of chronic GVHD: an international survey of the EBMT-NCI Chronic GVHD Task Force. *Bone Marrow Transpl*. 2014;49(1):49–54. https://doi.org/10.1038/bmt.2013.129.
7. Martin PJ, Inamoto Y, Carpenter PA, et al. Treatment of chronic graft-versus-host disease: Past, present and future. *Korean J Hematol*. 2011;46(3):153–163. https://doi.org/10.5045/kjh.2011.46.3.153.
8. Wolff D, Hilgendorf I, Wagner-Drouet E, et al. 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. *Biol Blood Marrow Transpl*. 2019;25(7):1450–1455. https://doi.org/10.1016/j.bbmt.2019.03.003.
9. Jagasia M, Scheid C, Socié G, et al. Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD. *Blood Adv*. 2019;3(14):2218–2229. https://doi.org/10.1182/bloodadvances.2019000145.
10. Zeiser R, Polverelli N, Ram R, Locatelli F, et al. REACH3 Investigators. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *N Engl J Med*. 2021;385(3):228–238. https://doi.org/10.1056/NEJMoa2033122.
11. Curtis LM, Ostojic A, Venzon DJ, et al. A randomized phase 2 trial of pomalidomide in subjects failing prior therapy for chronic graft-versus-host disease. *Blood*. 2021;137(7):896–907. https://doi.org/10.1182/blood.2020006892.
12. Pidala J, Bhatt VR, Hamilton B, et al. Ixazomib for Treatment of Refractory Chronic Graft-versus-Host Disease: A Chronic GVHD Consortium Phase II Trial. *Biol Blood Marrow Transpl*. 2020;26(9):1612–1619. https://doi.org/10.1016/j.bbmt.2020.05.015.
13. Kattner AS, Holler E, Holler B, et al. IL6-receptor antibody tocilizumab as salvage therapy in severe chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. *Ann Hematol*. 2020;99(4):847–853. https://doi.org/10.1007/s00277-020-03968-w.
14. Nahas MR, Soiffer RJ, Kim HT, Alyea 3rd EP, Arnason J, Joyce R, Antin JH, Ho VT, Stroopinsky D, Li S, Levine JD, McMasters M, Jain S, Hamdan A, Tzachanis D, Bryant MP, Logan EK, Bazemore J, Stewart J, Joyce A, Stephenson S, Washington A, Cole L, Pyzer A, Leaf RK, Avigan DE, Rosenblatt J. Phase 1 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease. *Blood*. 2018;131(25):2836–2845. https://doi.org/10.1182/blood-2017-05-780239.
15. Wertheimer T, Dohse M, Afram G, et al. Abatacept as salvage therapy in chronic graft-versus-host disease-a retrospective analysis. *Ann Hematol*. 2021;100(3):779–787. https://doi.org/10.1007/s00277-021-04434-x.
16. Fante MA, Holler B, Weber D, et al. Cyclophosphamide for salvage therapy of chronic graft-versus-host disease: a retrospective analysis. *Ann Hematol*. 2020;99(9):2181–2190. https://doi.org/10.1007/s00277-020-04193-1.
17. FDA expands ibrutinib indications to chronic GVHD. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ibrutinib-indications-chronic-gvhd. Accessed: March 10, 2025.
18. Martini DJ, Chen YB, DeFilipp Z. Recent FDA Approvals in the Treatment of Graft-Versus-Host Disease. *Oncologist*. 2022;27(8):685–693. https://doi.org/10.1093/oncolo/oyac076.
19. Wolf A, Masow J, Billings M. Novartis receives European Commission approval for Jakavi® to be the first post-steroid treatment for acute and chronic graft-versus-host disease; 2022. https://www.novartis.com/news/media-releases/novartis-receives-european-commission-approval-jakavi-be-first-post-steroid-treatment-acute-and-chronic-graft-versus-host-disease. Accessed: September 20, 2024.
20. Cutler C, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. *Blood*. 2021;138(22):2278–2289. https://doi.org/10.1182/blood.2021012021.

21. Wolff D, Cutler C, Lee SJ, et al. AGAVE-201 Investigators. Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease. *N Engl J Med*. 2024;391(11):1002–1014. https://doi.org/10.1056/NEJMoa2401537.
22. Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT (European Society for Blood and Marrow Transplantation) Transplant Complications Working Party and the "EBMT–NIH (National Institutes of Health)–CIBMTR (Center for International Blood and Marrow Transplant Research) GvHD Task Force". EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transpl*. 2018;53(11):1401–1415. https://doi.org/10.1038/s41409-018-0204-7.
23. Williams KM, Cheng GS, Pusic I, et al. Fluticasone, Azithromycin, and Montelukast Treatment for New-Onset Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplantation. *Biol Blood Marrow Transpl*. 2016;22(4):710–716. https://doi.org/10.1016/j.bbmt.2015.10.009.
24. Arai S, Arora M, Wang T, et al. Pavletic SZ; Graft-vs-Host Disease Working Committee of the CIBMTR. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transpl*. 2015;21(2):266–274. https://doi.org/10.1016/j.bbmt.2014.10.021.
25. Grube M, Holler E, Weber D, et al. Risk Factors and Outcome of Chronic Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation-Results from a Single-Center Observational Study. *Biol Blood Marrow Transpl*. 2016;22(10):1781–1791. https://doi.org/10.1016/j.bbmt.2016.06.020.
26. Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transpl*. 2014;49(2):168–173. https://doi.org/10.1038/bmt.2013.107.
27. Ruutu T, van Biezen A, Hertenstein B, et al. Prophylaxis and treatment of GVHD after allogeneic haematopoietic SCT: a survey of centre strategies by the European Group for Blood and Marrow Transplantation. *Bone Marrow Transpl*. 2012;47(11):1459–1464. https://doi.org/10.1038/bmt.2012.45.
28. Penack O, Marchetti M, Aljurf M, et al. Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol*. 2024;11(2):e147–e159. https://doi.org/10.1016/S2352-3026(23)00342-3.
29. Giaccone L, Mancini G, Mordini N, et al. Real-life' report on the management of chronic GvHD in the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Bone Marrow Transpl*. 2018;53(1):58–63. https://doi.org/10.1038/bmt.2017.223.
30. Axt L, Naumann A, Toennies J, et al. Retrospective single center analysis of outcome, risk factors and therapy in steroid refractory graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Bone Marrow Transpl*. 2019;54(11):1805–1814. https://doi.org/10.1038/s41409-019-0544-y.
31. Wolff D, Fatobene G, Rocha V, et al. Steroid-refractory chronic graft-versus-host disease: treatment options and patient management. *Bone Marrow Transpl*. 2021;56(9):2079–2087. https://doi.org/10.1038/s41409-021-01389-5.
32. Garnett C, Apperley JF, Pavlů J. Treatment and management of graft-versus-host disease: improving response and survival. *Ther Adv Hematol*. 2013;4(6):366–378. https://doi.org/10.1177/2040620713489842.
33. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125(4):606–615. https://doi.org/10.1182/blood-2014-08-551994.
34. Redondo S, Esquirol A, Novelli S, et al. Efficacy and Safety of Ruxolitinib in Steroid-Refractory/Dependent Chronic Graft-versus-Host Disease: Real-World Data and Challenges. *Transpl. Cell Ther*. 2022;28(1):43.e1–43.e5. https://doi.org/10.1016/j.jtct.2021.10.015.
35. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29(10):2062–2068. https://doi.org/10.1038/leu.2015.212.
36. Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. 2008;112(7):2667–2674. https://doi.org/10.1182/blood-2008-03-141481.
37. Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood*. 1998;92(9):3098–3104.
38. Kanold J, Merlin E, Halle P, et al. Photopheresis in pediatric graft-versus-host disease after allogeneic marrow transplantation: clinical practice guidelines based on field experience and review of the literature. *Transfusion*. 2007;47(12):2276–2289. https://doi.org/10.1111/j.1537-2995.2007.01469.x.
39. Zhao Y, OuYang G, Shi J, et al. Salvage Therapy With Low-Dose Ruxolitinib Leads to a Significant Improvement in Bronchiolitis Obliterans Syndrome in Patients With cGVHD After Allogeneic Hematopoietic Stem Cell Transplantation. *Front Pharmacol*. 2021;12:668825. https://doi.org/10.3389/fphar.2021.668825.
40. DeFilipp Z, Kim HT, Cheng GS, et al. A phase 2 multicenter trial of ruxolitinib to treat bronchiolitis obliterans syndrome after allogeneic HCT. *Blood Adv*. 2024. https://doi.org/10.1182/bloodadvances.2024014000.
41. Koshy AG, Kim HT, Liegel J, et al. Phase 2 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease. *Blood*. 2023;141(24):2932–2943. https://doi.org/10.1182/blood.2022019107.
42. DeFilipp Z, Kim HT, Yang Z, et al. Clinical response to belumosudil in bronchiolitis obliterans syndrome: a combined analysis from 2 prospective trials. *Blood Adv*. 2022;6(24):6263–6270. https://doi.org/10.1182/bloodadvances.2022008095.