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

Olaf Penack, Monia Marchetti*, Mahmoud Aljurf, Mutlu Arat, Francesca Bonifazi, Rafael F Duarte, Sebastian Giebel, Hildegard Greinix, Mette D Hazenberg, Nicolaus Kröger, Stephan Mielke, Mohamad Mohty, Arnon Nagler, Jakob Passweg, Francesca Patriarca, Tapani Ruutu, Hélène Schoemans, Carlos Solano, Radovan Vrhovac, Daniel Wolff, Robert Zeiser, Anna Sureda, Zinaida Peric*

Graft-versus-host disease (GVHD) is a major factor contributing to mortality and morbidity after allogeneic haematopoietic stem-cell transplantation (HSCT). In the last 3 years, there has been regulatory approval of new drugs and considerable change in clinical approaches to prophylaxis and management of GVHD. To standardise treatment approaches, the European Society for Blood and Marrow Transplantation (EBMT) has updated its clinical practice recommendations. We formed a panel of one methodologist and 22 experts in the field of GVHD management. The selection was made on the basis of their role in GVHD management in Europe and their contributions to the field, such as publications, presentations at conferences, and other research. We applied the GRADE process to ten PICO (patient, intervention, comparator, and outcome) questions: evidence was searched for by the panel and graded for each crucial outcome. In two consensus meetings, we discussed the evidence and voted on the wording and strengths of recommendations. Key updates to the recommendations include: (1) primary use of ruxolitinib in steroid-refractory acute GVHD and steroid-refractory chronic GVHD as the new standard of care, (2) use of rabbit anti-T-cell (thymocyte) globulin or post-transplantation cyclophosphamide as standard GVHD prophylaxis in peripheral blood stem-cell transplantations from unrelated donors, and (3) the addition of belumosudil to the available treatment options for steroid-refractory chronic GVHD. The EBMT proposes to use these recommendations as the basis for routine management of GVHD during allogenic HSCT. The current recommendations favour European practice and do not necessarily represent global preferences.

Introduction

One of the main clinical challenges of allogeneic haematopoietic stem-cell transplantation (HSCT) is its inherent treatment-associated morbidity and mortality with graft-versus-host disease (GVHD) as a major contributing factor. The European Society for Blood and Marrow Transplantation (EBMT) last updated its clinical practice recommendations in 2018 and 2019 and published them in early 2020.[1] Since then, new GVHD treatment options became available. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved ruxolitinib, an inhibitor of Janus kinase 2 (JAK2), for treatment of steroid refractory acute GVHD (SR-aGVHD) and steroid refractory chronic GVHD (SR-cGVHD). In addition, the FDA approved belumosudil for treatment of SR-cGVHD, which is an inhibitor of Rho-associated coiled-coil-containing protein kinase 2 (ROCK2). Also, the prevention strategies of GVHD are currently changing. Cyclophosphamide given after allogenic HSCT (post-transplant cyclophosphamide [PTCy]) is increasingly used in many transplantation centres, but no formal recommendations are available.

The EBMT decided to update the recommendations on the management of GVHD in 2022. Similar to the previous guidelines, the present recommendations on GVHD prophylaxis exclusively apply to the most common allogeneic transplantation settings in Europe. This Review focuses on allogenic HSCT for haematological malignant disease in adult patients using unrelated donors or HLA-matched related donors and bone marrow or peripheral blood as the stem-cell source. There are divergent views concerning GVHD prophylaxis in paediatric transplantations, haploidentical transplantations, and transplantations using cord blood as the donor source. The current recommendations favour European practice and do not necessarily represent global preferences.

Methods

In the current guideline recommendation process, we selectively updated our previous guidelines. The methodology of the previous guidelines has been published.[1] The panels in this Review contain the key recommendations that are still valid and were not updated to facilitate the use for the reader. The National Comprehensive Cancer Network (NCCN) classification of evidence and consensus was modified, replacing category 3 recommendations (not approved) with category 2C recommendations (not directly supported by evidence). Category 1 includes recommendations based on high-level evidence (randomised trials or meta-analyses) and 100% consensus after a second round, category 2A includes recommendations based on lower-level evidence and 100% consensus after a second round, category 2B includes recommendations based on lower-level evidence and 80–100% consensus

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*Contributed equally

Department of Hematology, Oncology and Tumorimmunology, Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Berlin, Germany (Prof O Penack MD); **Hematology Service, Oncology Unit, Hospital Cardinal Massaia, Asti, Italy** (M Marchetti MD); **Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia** (Prof M Aljurf MD); **Istanbul Florence Nightingale Hospital, Stem Cell Transplantation Unit, Istanbul, Türkiye** (Prof M Arat MD); **IRCCS Azienda Ospedaliero, Universitaria di Bologna, Bologna, Italy** (Prof F Bonifazi MD); **Hematopoietic Transplantation and Hemato-Oncology Section, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain** (Prof R F Duarte MD); **Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland** (Prof S Giebel MD); **Division of Hematology, Medical University Graz, Auenbruggerplatz, Graz, Austria** (Prof H Greinix MD); **Department of Hematology, Amsterdam University Medical Centers, University of Amsterdam, Netherlands** (Prof M D Hazenberg MD); **University Medical Center Hamburg, Hamburg, Germany** (Prof N Kröger MD); **Karolinska Instituet and University Hospital, Department of Laboratory Medicine, Cell Therapy and Allogenic Stem Cell Transplantation (CAST), Stockholm, Sweden** (Prof S Mielke MD); **Department**

of Haematology, Hôpital Saint-Antoine, Sorbonne University, Institut National de la Santé et de la Recherche Médicale (INSERM) Paris, France (Prof M Mohty MD); Hematology and Bone Marrow Transplant, Chaim Sheba Medical Center, Tel Hashomer, Israel (Prof A Nagler MD); Hematology Division, University Hospital, Basel, Switzerland (Prof J Passweg MD); Haematological Clinic and Transplant Centre, University Hospital of Central Friuli, Dipartimento Area Medica, University of Udine, Udine, Italy (Prof F Patriarca MD); Helsinki University Hospital Comprehensive Cancer Center and Clinical Research Institute, Helsinki University Hospital, Helsinki, Finland (Prof T Ruutu MD); Department of Hematology, University Hospitals Leuven, Leuven, Belgium (Prof H Schoemans MD); Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery (AccentVV), KU Leuven, Leuven, Belgium (Prof H Schoemans); Hematology Department, Hospital Clínico Universitario – INCLIVA, University of Valencia, Valencia, Spain (Prof C Solano MD); Department of Haematology, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia (Prof R Vrhovac MD, Prof Z Peric MD); Medical Clinic 3, Haematology and Oncology, Klinikum der Universität Regensburg, Regensburg, Germany (Prof D Wolff MD); Department of Hematology, Oncology and Stem Cell Transplantation, Faculty of Medicine, Freiburg University Medical Center, Freiburg, Germany (Prof R Zeiser MD); Clinical Hematology Department, Institut Català d'Oncologia-Hospitalet, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), University of Barcelona, Barcelona, Spain (Prof A Sureda MD)

after a second round, and category 2C includes recommendations not supported by direct evidence, but rather included in published and adopted clinical protocols.

Expert panel

An expert panel of 22 allogeneic transplantation physicians from centres in 15 countries (Austria, Belgium, Croatia, Finland, France, Germany, Israel, Italy, Poland, Saudi Arabia, Spain, Sweden, Switzerland, the Netherlands, and Türkiye) was convened and guided by a Chair (OP) and a methodologist (MMa). We feel that expert selection for clinical practice guidelines is still an imperfect process, therefore the process was principally guided by the methodologist and conflict of interests were managed as reported later.[2] The choice of experts was initially suggested by OP (Chairperson of the Guideline Committee) on the basis of their role in the GVHD field in Europe reflected by contributions made, such as publications, presentations at conferences, and other research. The choice of experts was approved by AS (EBMT President), ZP (Chair for the Transplant Complications Working Party) and MMa (methodologist).

Clinical questions and the GRADE process

The current process is a selective update of previous guidelines focussing on PTCy prophylaxis and therapy with ruxolitinib, belumosudil, and ibrutinib.[1] For the current update, we phrased seven clinical questions: which adult patients undergoing ([1] matched related donor [MRD], [2] matched unrelated donor [MUD], or [3] mismatched unrelated donor [MMUD: one antigen mismatch]) allogenic HSCT benefit from PTCy as GVHD prophylaxis, (4) which patients with SR-aGVHD benefit from ruxolitinib treatment, or which patients with SR-cGVHD benefit from ([5] ruxolitinib, [6] ibrutinib, or [7] belumosudil) treatment? We then translated these questions into ten patient, intervention, comparator, and outcome (PICO) questions and produced clinical recommendations by a GRADE process (grading of recommendations, assessment, development, and evaluations).[3] PICOs are listed in the appendix (p 1). Crucial outcomes (ie, GVHD overall response rate, non-relapse mortality, and failure-free survival) and important outcomes (ie, incidence of relapse and GVHD-free and relapse-free survival) were chosen on the basis of the panellists' expertise and the Canadian Agency for Drugs and Technologies in Health landmark analysis.

Rating of crucial outcomes

According to the GRADE process, the expert panel rates the differences in favourable and unfavourable crucial outcomes reported for patients receiving the intervention rather than the comparator therapy. The experts were therefore asked to rate as "trivial", "small", "moderate", or "large", the effect of a hypothetical "intervention" (*vs* a hypothetical "comparator") on overall response rate of cGVHD, 2-year cumulative relapse rate, 2-year non-relapse mortality, and 2-year GVHD-free and relapse-free survival. Overall, 32 scenarios were graded and thresholds defined by more than 50% of the votes (appendix p 2).

GRADE process

The body of evidence was retrieved and appraised by the methodologist and presented to a Chair and Co-chair, who revised the evidence and proposed a recommendation for each PICO. Direction, strength, and wording of recommendations were discussed and voted for by the full expert panel in two virtual meetings (on March 22, 2023, and March 23, 2023; appendix p 3). Subgroup or implementation issues (including economic or equity issues) were raised during the plenary meetings and reported in the body of the text.

Management of conflicts of interest

The National Academy of Medicine (IOM) defined conflicts of interest (COI) as: "circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest". For guideline development, panellists' secondary (financial and non-financial) interests might influence interpretation of the evidence and voting of recommendations.[4] Therefore, before starting the project we asked all the panellists to disclose their potential COIs (standard 2.1 and 2.2a IOM). Most of the panellists declared financial and non-financial COIs with different pharmaceutical companies producing some of the drugs discussed in the revised recommendations (standard 2.4 IOM not met). Therefore, panellists reporting major COIs, such as being a principal investigator for registrative trials, were not selected for their role of drug specific PICOs. Moreover, panellists were able to avoid voting for specific recommendations if a COI was judged as interfering, as requested by the GRADE process and standard 2.2b IOM. Furthermore, the methodologist co-chair (who was free of relevant COIs) primarily guided the meetings to mitigate the potential bias in the present consensus guidelines. Finally, most recommendations were heavily evidence-based, which safeguard from potential interference of COIs.

Definitions

To define aGVHD during the consensus process, we used the criteria established by the MAGIC group.[5] To define cGVHD, we used the National Institutes of Health (NIH) 2014 criteria.[6] Steroid resistance and dependence in aGVHD and cGVHD was defined as described in the EBMT–NIH–CIBMTR (Center for International Blood and Marrow Transplant Research) Task Force position statement.[7]

Results

Consensus recommendations for prophylaxis of GVHD

In the last few years there has been a change of practice towards an increasing use of PTCy as GVHD prophylaxis

Panel 1: Recommendations on prophylaxis of graft-versus-host disease

New recommendations

- For recipients of allogeneic haematopoietic stem-cell transplantation (HSCT) from a matched related donor (MRD), post-transplantation cyclophosphamide (PTCy) should not be generally preferred to rabbit anti-T-cell globulin (rATG) for preventing GVHD (National Comprehensive Cancer Network [NCCN] classification 2A)
  - Acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD) reduction was consistently reported by moderate quality evidence for PTCy compared with prevention without ATG,[8–15] but only indirect comparative evidence suggests similar outcomes of PTCy as compared with ATG[16–19]
- For recipients of allogenic HSCT from a matched unrelated donor (MUD), GVHD prophylaxis including rATG or PTCy should be preferred to prophylaxis with neither rATG nor PTCy (NCCN classification 1)
  - High-quality consistent evidence from randomised controlled trials supported the reduced incidence of severe aGVHD and severe cGVHD, and improved GVHD-free, relapse-free survival when PTCy is used instead of immunosuppression without rATG[8–11]
  - Reduction of cGVHD had also been reported by randomised studies comparing rATG with an immunosuppressive drug[12,13]
  - Comparative evidence of ATG versus PTCy consists of two low-quality randomised trials, one meta-analysis, and several large retrospective studies showing similar crucial outcomes for both prophylaxis strategies[14–16]
- For recipients of allogenic HSCT from mismatched unrelated donors (MMUD), GVHD prophylaxis including rATG or PTCy should be preferred to prophylaxis with neither rATG nor PTCy (NCCN classification 2A)
  - Moderate quality comparative evidence of ATG versus PTCy, including a meta-analysis, suggests a possible amelioration of non-relapse mortality with PTCy, but the residual uncertainty does not allow to favour one strategy over another[17–19]

Recommendations published previously[1] without the need to update

- rATG (Thymoglobulin or Grafalon) is recommended for preventing GVHD in patients undergoing MUD allogeneic HSCT (NCCN classification 1)
  - Reduction of cGVHD in randomised studies[12,13,20]
- rATG can be recommended for preventing GVHD in patients undergoing MRD allogeneic peripheral blood stem-cell transplantation (NCCN classification 2B)
  - Reduction of cGVHD in randomised studies and retrospective analyses[21–23]
- Patients undergoing MRD or MUD allogeneic transplantation should receive GVHD prophylaxis with a calcineurin inhibitor (CNI) plus an antimetabolite (NCCN classification 1)
  - Reduction of aGVHD with methotrexate (MTX) plus cyclosporine A (CsA) versus CsA in several trials[24–26]
- Tacrolimus or CsA can be used in the setting of sibling or MUD transplants. The choice should be based on the centre experience (ie, CsA is the standard CNI adopted in most European centres; NCCN classification 1).
  - Similar GVHD and survival outcome with tacrolimus (plus MTX) versus CsA (plus MTX) from randomised trials and several retrospective controlled studies[27–30]
- MTX is the recommended antimetabolite for patients receiving myeloablative conditioning (NCCN classification 1)
  - Meta-analyses and retrospective studies reported similar grade 2–4 GVHD and survival rates with MTX (plus CNI) as compared with mycophenolate mofetil (MMF; plus CNI); however, higher grade 3–4 GVHD rates were reported with MMF[31–34]
- MMF can be used instead of MTX for patients receiving myeloablative conditioning (MAC) in case of contraindications to MTX or for patients who need rapid engraftment (ie, those with aspergillosis; NCCN classification 2A)
  - Meta-analyses and retrospective studies reported similar grade 2–4 GVHD and survival rates with MTX (plus CNI) as compared with MMF (plus CNI); however, higher grade 3–4 GVHD rates were reported with MMF[31–34]
- MMF is the recommended antimetabolite for patients receiving non-MAC and reduced-intensity conditioning (NCCN classification 2A)
  - Common practice based on the initial developed protocol. Comparative evidence for MMF versus MTX in the NMA setting is absent

Correspondence to:
Prof Olaf Penack, Department of Hematology, Oncology and Tumorimmunology, Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Berlin 13353, Germany
olaf.penack@charite.de

See Online for appendix

For the **Canadian Agency for Drugs and Technologies in Health reimbursement recommendation of ruxolitinib** see https://canjhealthtechnol.ca/index.php/cjht/article/download/SR0706/826?inline=1

outside the classic use in haploidentical allogenic HSCT. This aspect was not covered in the previous EBMT guidelines, where rabbit anti-thymocyte globulin or anti-T-lymphocyte globulin (both termed rATG) use was recommended as GVHD prophylaxis.[1] We developed recommendations on PTCy use in the different transplant settings: (1) allogenic HSCT from MRDs, (2) alloSCT from MUDs, and (3) alloSCT from MMUDs (panel 1).

We aimed to find if we could recommend PTCy instead of no PTCy or rATG in recipients of allogenic HSCT from MRDs to prevent GVHD and reduce non-relapse mortality. Four randomised studies comparing PTCy prophylaxis versus no PTCy (without ATG) also enrolled recipients of MRD allogenic HSCT.[8–11] The incidence of both aGVHD and cGVHD was significantly reduced with PTCy in patients enrolled by the CTN 1703 trial (grade 3–4

aGVHD at day 100 was 6·3% *vs* 14·7%; p<0·001; cGVHD at 1 year was 21·9% *vs* 35·1%; p=0·005)[8] and in non-randomised studies[35–37] retrieved at systematic analysis (in the matched-pair, study grade 2–4 aGVHD at day 100 was 23% *vs* 57%; p<0·001; moderate to severe cGVHD at 1 year was 23% *vs* 49%; p=0·003).[36] No significant differences in non-relapse mortality after MRD allogenic HSCT with or without PTCy were reported in the EBMT matched retrospective study,[38] or MRD-specific subgroup analyses of retrospective cohorts.[11] Despite significant relapse rates (41% *vs* 21%; p=0·039) that were estimated in the PTCy group of the matched EBMT retrospective study,[38] improved GVHD-free and relapse-free survival was associated with PTCy use in the CTN 1703 (53% *vs* 35%; p=0·001) trial,[8] and in two large retrospective studies.[35,37] On the basis of these data, PTCy was considered a potential option for preventing GVHD instead of immunosuppression without rATG for recipients of allogenic HSCT from MRDs.

We were unable to find direct evidence comparing PTCy versus rATG prophylaxis in MRD allogenic HSCT since most of the reported populations included both MRDs and MUDs. The retrieved studies included a network meta-analysis,[39] a randomised trial (31 of 80 recipients of MRD allogenic HSCT),[14] and retrospective studies enrolling mostly recipients of MUD allogenic HSCT.[40,41] No significant difference in non-relapse mortality of PTCy-treated patients versus ATG was reported by these studies. No significant difference in the occurrence of GVHD was documented by the randomised trial[14] or by the EBMT retrospective study.[40] However, a favourable odds ratio in the PTCy group was shown by the network meta-analysis[39] and a significant decline of grade 2–4 aGVHD (hazard ratio [HR] 0·41; p=0·035) and moderate to severe cGVHD (HR 0·15; p<0·001), and a significant improvement of GVHD-free and relapse-free survival (50·2% *vs* 21·8% at 2 years; HR 0·42; p=0·001) were reported for PTCy by multivariate analysis in a retrospective study selectively enrolling patients older than 50 years.[41] The panel considered the indirect evidence (mainly based on data from MUD transplants) not sufficiently reliable to support practice-changing recommendations and therefore suggested that for recipients of allogenic HSCT from MRDs, PTCy should not be generally preferred to ATG for preventing GVHD. Based on these data, we consider PTCy a potential option for preventing GVHD over immunosuppression without rATG for recipients of allogenic HSCT from MRDs. This treatment option might be specifically applicable in settings where rATG is not available. However, we support our previous recommendations to use rATG as GVHD prophylaxis in patients undergoing MRD allogenic HSCT. The recommendations are based on high evidence by publications demonstrating reduced cGVHD rates in MRD allogenic HSCT.[20–23]

We then wanted to assess if we could recommend PTCy instead of no PTCy or rATG in allogenic HSCT recipients from MUDs to prevent GVHD and reduce non-relapse mortality. Several studies, including four randomised controlled trials, compared PTCy prophylaxis with no PTCy (without rATG) in MUD allogenic HSCT.[8–11] The incidence of both severe aGVHD and severe cGVHD was significantly reduced in both the CTN 1703 and HOVON-96 randomised trials: the HR of multivariate analysis from the HOVON-96 trial was 0·48 (95% CI 0·29–0·82) for aGVHD and 0·36 (0·21–0·64) for cGVHD.[10] No significant differences in non-relapse mortality after MUD allogenic HSCT with or without PTCy were reported, but both the randomised trials showed significantly improved GVHD-free and relapse-free survival associated with PTCy use with an HR of 0·50 (95% CI 0·34–0·74) in the HOVON-96 trial[10] and 0·64 (95% CI 0·49–0·84) in the CTN 1703 trial.[8] Of note, the HOVON-96 trial has several caveats: it was initially designed as a two-group study comparing two different durations of immunosuppression with mycophenolate mofetil (MMF) and cyclosporine A, and PTCy was only introduced as a third group after study initiation. The primary endpoint was non-severe GVHD at day 180 (defined as aGVHD grade 1, aGVHD grade 2 without gut involvement, or cGVHD not requiring systemic treatment [not NIH consensus criteria]). Furthermore, many centres use sirolimus in addition to cyclosporine A and MMF after non-myeloablative MUD allogenic HSCT, whereas the control group of the HOVON-96 trial used cyclosporine A and MMF without sirolimus. Nevertheless, the panel considered the total body of evidence sufficient to recommend that PTCy should be preferred to GVHD prophylaxis without rATG in recipients of allogenic HSCT from MUDs.

The body of evidence comparing PTCy versus rATG included two randomised trials,[14,15] a moderate quality meta-analysis,[16] and several large retrospective studies. One randomised trial did not report any significant difference in the major outcomes of the 80 patients assigned to either PTCy or rATG prophylaxis in MUD or MRD transplantation; however, no subgroup analysis was provided for MUD allogenic HSCT.[14] The other randomised trial was interrupted early after enrolment of 33 patients.[15] A recent EBMT analysis in MUD allogenic HSCT recipients with acute lymphoblastic leukaemia found a reduced risk of severe cGVHD and inferior leukaemia free survival when rATG was used in comparison to PTCy. These data underline that disease-specific considerations are of importance in clinical practice.[42] One meta-analysis pooled the results of six retrospective studies enrolling a total of 2379 patients receiving either PTCy or rATG for GVHD prophylaxis after MUD allogenic HSCT: lower rates of grade 2–4 aGVHD (risk ratio [RR] 0·68; 95% CI 0·50–0·93), lower rates of non-relapse mortality (RR 0·67; 0·53–0·84), and higher overall survival (RR 1·29; 1·03–1·62) were reported with PTCy.[16] Evidence for cGVHD was contradictory and no statistically significant advantage

of PTCy was reported from the meta-analysis.[16] The GVHD-free and relapse-free survival was significantly ameliorated on multivariate analysis of some large retrospective studies, but not in others.[40,41]

Based on these data and long-term outcomes with rATG in MUD allogenic HSCT,[12,13] we provided the following recommendations: (1) rATG (Thymoglobulin or Grafalon) is recommended for preventing GVHD, (2) GVHD prophylaxis including PTCy might be used as an alternative to prophylaxis with rATG, and (3) GVHD prophylaxis including rATG or PTCY should be preferred to prophylaxis with neither rATG nor PTCy.

Of note, the studies comparing PTCy with rATG or PTCy with no rATG were heterogeneous regarding the type of conditioning used and some included bone marrow as a donor stem cell source. This aspect was too complex to include into formal recommendations. However, we would like to highlight that PTCy was often used with dose-reduced conditioning regimens in contrast to cyclosporine A in combination with methotrexate, which is typically used with myeloablative regimens (appendix pp 4–5).

We aimed to find if we could recommend PTCy instead of no PTCy or rATG in recipients from a MMUD to prevent GVHD and reduce non-relapse mortality. The standard of care has been to use rATG in allogenic HSCT from MMUDs in Europe and there is no direct evidence available on PTCy prophylaxis versus no rATG use. A few MMUD patients (with a 7/8 HLA match) were enrolled in the CTN 1703 and CTN 1203 randomised trials,[8,9] and in comparative retrospective studies.[43]

No randomised trials specifically compared PTCy with rATG prophylaxis in MMUD allogenic HSCT, but two retrospective studies and a meta-analysis dedicated to this specific population showed no significant reduction in the incidence or severity of aGVHD or cGVHD in patients receiving PTCy, while a decreasing rate was estimated after adjusting for propensity.[17–19] The meta-analysis[18] highlighted a reduced NRM in the PTCy group (8·6% at median 2·6 years; 95% CI 4–14%) versus rATG (26·3% at median 3 years; 20–33%), which supports the results of a propensity-adjusted retrospective study.[43] However, the GVHD-free and relapse-free survival was not significantly ameliorated in the EBMT retrospective cohort.[19] Based on these data and increasing non-comparative evidence,[44,45] we recommend the following: (1) rATG (Thymoglobulin or Grafalon) or PTCy are recommended for preventing GVHD in patients undergoing MMUD allogenic HSCT, and (2) GVHD prophylaxis including rATG or PTCy should be preferred to prophylaxis with neither rATG nor PTCy.

Statement on abatacept for prophylaxis of GVHD

Recently, abatacept has been approved for GVHD prophylaxis in the USA by the FDA. Abatacept is a recombinant soluble fusion protein that inhibits antibody-dependent, cell-mediated cytotoxicity and complement fixation by blocking the downstream activation mediated by costimulatory molecule CTL4, and co-stimulation CTLA4. The randomised (double-blind placebo-controlled) phase 2 ABA2 study reported post-transplant outcomes in 112 patients (both adults and children) receiving allogenic HSCT (with myeloablative conditioning therapy in 73%) from either matched unrelated (69 patients) or mismatched (7/8 match of 43 patients) donors (peripheral blood stem cells in 58% and T-cell repleted grafts in all patients). Patients with matched donors were assigned to standard calcineurin inhibitor plus methotrexate and randomised to also receive abatacept or placebo. Abatacept was administered at 10 mg per kg (bodyweight) intravenously in four doses on day minus 1 then days 5, 8, and 14. In the MUD subgroup, no significant reduction of aGVHD was documented in abatacept-treated patients as compared with placebo (grade 3–4 aGVHD 6·8% *vs* 14·8%, p=0·13). However, in the mismatched donor subgroup, grade 3–4 aGVHD was rare (2·3%) in patients treated with abatacept, while in a pre-specified registry cohort from CIBMTR the rate was 30·2% (p<0·001). In the same subgroup, the cumulative incidence of cGVHD was 57·9% and 2-year cumulative incidence of transplant-related mortality was 16·1%. Moreover, cumulative incidence of relapse was 9·3%, GVHD-free and relapse-free survival was 34·9% at 1 year, and overall survival at 2 years was 73·6%.[46] In addition, a possible survival advantage is hypothesised for abatacept (*vs* ATG or PTCy) from real-life data in 216 mismatched donor recipients recorded by CIBMTR.[47] The panel did not judge the direct evidence for abatacept versus standard of care (immunosuppression with or without ATG) sufficient to support a formal recommendation for standard of care in Europe. In particular, the small subgroup of mismatched donors was not compared with a placebo group. Moreover, adults and children were concurrently enrolled and more importantly, no clinically relevant advantage was shown in the larger set of MUDs. Conversely, the body of evidence supporting the efficacy of PTCy in the MMUD setting is consistently growing.[48] The panel therefore expect to be able to provide formal recommendations in the next revision of the present guideline.

Consensus recommendations for treatment of SR-aGVHD

Since the last EBMT GVHD recommendations were published, the results of a randomised controlled trial has led to EMA and FDA approval of ruxolitinib. We have therefore specifically updated our recommendations (panel 2). In adults with SR-aGVHD, we wanted to find if ruxolitinib should be used instead of additional immunosuppressive agents to ameliorate GVHD severity, reduce non-relapse mortality, or improve failure-free survival. As an evidence base we identified one randomised trial (REACH 2),[49] and three meta-analyses.[50–52] In the randomised trial, the overall response

***Panel* 2: Recommendations on aGVHD treatment**

New recommendations

- In adults with steroid-refractory acute graft-versus-host disease (SR-aGVHD) we recommend ruxolitinib (National Comprehensive Cancer Network [NCCN] classification 1)
  - Large beneficial effect on overall response rate and failure-free survival in a randomised trial and three meta-analyses, with no relevant increase of undesirable effects[49-52]

Recommendations published previously[1] without need for update

- The decision to initiate treatment for aGVHD is on the basis of clinical signs. Biopsies before initiation of treatment are recommended, but the decision to treat should not be delayed until after histology reporting (NCCN classification 2C).
  - Recommendation is supported by standard practice and expert opinion
- Systemic treatment is initiated for aGVHD of grade 2 or higher (NCCN classification 1)
  - More infections and no advantage regarding development of grade 3–4 aGVHD when grade 1 aGVHD was treated in a randomised trial[53]
- First-line treatment of aGVHD is methylprednisolone with an initial dose of 2 mg per kg daily. Prednisone at 2·0–2·5 mg per kg daily is regarded as equivalent to methylprednisolone (NCCN classification 1).
  - A meta-analysis of seven randomised trials reported a 14% decrease of survival in patients receiving additional immunomodulating agents (mycophenolate mofetil, anti-T-cell globulin, infliximab, or anti-IL2 antibody) besides steroids.[54] Higher methylprednisolone doses (10 mg per kg daily day) did not improve outcomes as compared with standard 2 mg per kg daily.[55]
- Grade 2 aGVHD with isolated skin or upper gastrointestinal tract manifestations can be treated with lower steroid doses, such as 1 mg per kg daily methylprednisolone or prednisone (NCCN classification 1)
  - Retrospective analyses and randomised trial showed efficacy of 1 mg per kg daily of prednisone[56,57]
- No reduction of the dose is recommended during the first 7 days, but parenteral steroids can be discontinued, and oral steroids can be used until all signs of aGVHD have disappeared. Tapering of the dose is done slowly and depending on response: in case of complete response, steroid dose should be gradually reduced to 10% of the initial dose in approximately 4 weeks. In case of steroid-resistant GVHD, long term use of steroids might cause major complications, therefore, second-line therapy is recommended (NCCN classification 1).
  - Recommendation made from statements largely based on expert opinion. One small randomised trial found no significant differences between rapid steroid taper and slower steroid taper.[58]
- Topical steroids are sufficient for grade 1 skin aGVHD. In case of more advanced disease, they can be used in addition to systemic treatment, when needed (NCCN classification 2C).
  - Recommendation made from standard practice and expert opinion
- Non-absorbable oral steroids, like budesonide (9 mg per day) or oral beclomethasone (1·3–2·0 mg four times a day), can be given in addition to systemic corticosteroids as treatment of gastrointestinal tract aGVHD (NCCN classification 1)
  - Two small randomised trials in patients with systemic steroids for gastrointestinal tract aGVHD tested beclomethasone 8 mg per day versus placebo and found favourable treatment responses and reduced mortality[59,60]
- A second-line treatment for aGVHD is recommended if corticosteroid resistance or dependence occurs (NCCN classification 2C)
  - Recommendation made from standard practice and expert opinion

rate of aGVHD was 55% in the ruxolitinib group versus 39% in the best available therapy control group. Data from the meta-analyses were in the same range. We considered the improvement as a large beneficial effect (appendix p 2). Conversely, non-relapse mortality was not different in patients treated with ruxolitinib versus control. Failure-free survival at 1 month and at 18 months was consistently superior in ruxolitinib-treated patients with SR-aGVHD. Of note, the control group in the randomised trial did not receive abatacept, which is a new treatment option. Taken together, one prospective randomised trial and pooled data from several retrospective studies showed higher overall and complete response rates and improved failure-free survival. The body of evidence was of moderate quality. Non-relapse mortality did not change and no relevant worsening of haematological or non-haematological toxicity was described. Based on these considerations, we strongly recommend ruxolitinib as primary treatment in patients with SR-aGVHD.

No difference in response rates or survival after ruxolitinib therapy was described regarding organ involvement of SR-aGVHD. Due to the known haemotoxicity of ruxolitinib (not found in the REACH 2 trial), we recommend using ruxolitinib with caution in patients with severe cytopenia or severe uncontrolled infections. Ruxolitinib is an oral agent and absorption in GVHD patients with severe aGVHD-related diarrhoea might be reduced.

***Panel 3*: Recommendations on cGVHD treatment**

New recommendations

- In adults with steroid-refractory chronic graft-versus-host disease (SR-cGVHD), we recommend ruxolitinib (National Comprehensive Cancer Network [NCCN] classification 1)
  - Large beneficial effect on overall response rate and failure-free survival in a randomised trial, a propensity-adjusted retrospective analysis, and three meta-analyses[50–52,61,62]
- In adults with SR-cGVHD, belumosudil is a potential therapeutic option (NCCN classification 2C)
  - Encouraging overall response rates in non-randomised trials showing a low drug induced toxicity profile[63–66]
- In adults with SR-cGVHD, ibrutinib is a potential therapeutic option (NCCN classification 2B)
  - Encouraging overall response rates in non-randomised trials in patients with moderate GVHD burden and an acceptable toxicity profile[67–71]

Recommendations on cGVHD treatment published previously[1] without need for update

- The decision to start treatment for cGVHD is made on the basis of symptom type, severity (moderate and severe according to National Institutes of Health, and dynamics of progression in the context of other relevant variables, such as disease risk, chimerism and minimal residual disease results (NCCN classification 2C)
  - Recommendation made from standard practice and expert opinion
- First-line treatment of newly diagnosed cGVHD is steroids (NCCN classification 2A)
  - Randomised trials evaluated the addition of other agents (azathioprine, cyclosporine, cyclosporine A, thalidomide, mycophenolate mofetil, or hydroxychloroquine) to prednisone and failed to show a clinically meaningful benefit in patients with cGVHD[72–74]
- In severe cGVHD, the primary addition of another immunosuppressant to spare steroids is a valuable option (NCCN classification 2C)
  - Recommendation made based on expert opinion
- The first-choice corticosteroid is prednisone at a dose of 1 mg per kg orally (NCCN classification 2C)
  - Recommendation made from standard practice and expert opinion
- If the patient is already on corticosteroid treatment (eg, following treatment of aGVHD), the dose of corticosteroid can be increased (if lower than 1 mg per kg) and an alternative strategy is usually applied, such as calcineurin inhibitor or extracorporeal photopheresis (NCCN classification 2C)
  - Recommendation made from standard practice and expert opinion
- If the patient is already receiving full-dose corticosteroid and cyclosporine A at the time of cGVHD onset, no standard treatment is available: continuation of corticosteroid and cyclosporine A with optimal supportive measures is a valid option but a change of immunosuppressive therapy is often applied. These patients should be treated in clinical trials, if possible (NCCN classification 2C).
  - Recommendation made based on expert opinion
- As initial treatment of bronchiolitis obliterans syndrome (BOS) the FAM regimen (fluticasone, azithromycin, and montelukast) is recommended in combination with systemic steroids. However, extended use of azithromycin after resolution of BOS is not recommended due to the possibility of increased risk of relapse (NCCN classification 2A).
  - There are encouraging data from non-randomised studies supporting the therapeutic use of FAM regimen (inhaled fluticasone 440 µg twice daily, azithromycin 250 mg three times weekly, and montelukast 10 mg daily).[75–77] In contrast, when used as prophylaxis in patients undergoing allogenic HSCT, azithromycin (250 mg thrice a week) was associated with increased relapse rates.[78]
- The time needed to preliminarily assess the efficacy of first-line treatment of cGVHD is at least one month (NCCN classification 2C)
  - Recommendation made based on expert opinion

Consensus recommendations for treatment of SR-cGVHD

Since the last EBMT GVHD recommendations were published, the results of a randomised controlled trial led to EMA and FDA approval of ruxolitinib. In addition, non-randomised trial data led to FDA (but not EMA) approval of ibrutinib and belumosudil for SR-cGVHD. We have therefore updated our recommendations on the use of ruxolitinib, belumosudil, and ibrutinib (panel 3).

We aimed to assess for adults with SR-cGVHD, if ruxolitinib should be used over additional immunosuppressive agents to ameliorate GVHD severity, reduce non-relapse mortality, or improve failure-free survival. The body of evidence included a randomised controlled trial of moderate quality (open label, crossover, and further limitations) comparing ruxolitinib with the best available therapy, that was extracorporeal photopheresis (ECP) in 32% of the patients, MMF in 22%, and ibrutinib in 17%.[61] In addition, the body of evidence also included a propensity score matched analysis[43] and three meta-analyses.[50–52]

The overall response rate of cGVHD was 49·7% in the ruxolitinib versus 25·6% in the control group, which we graded as a moderate effect, although more than half of patients enrolled in the REACH 3 trial had severe cGVHD at baseline. Evidence from meta-analyses pooling data from several retrospective real-life studies was consistent

with the trial results. Non-relapse mortality was not different in the randomised trial. Failure-free survival was 74·9% in ruxolitinib-treated patients versus 44·5% in the standard group of the REACH 3 trial and was consistent with the propensity-matched analysis and with the meta-analyses. We considered this as a large effect (appendix p 2). A similar rate of grade 3–4 adverse events but a higher discontinuation rate in ruxolitinib-treated patients (16·4% *vs* 7·0%) was reported in the randomised trial. These data were consistent with real-world evidence.

In summary, we graded the amelioration of crucial desirable outcomes caused by ruxolitinib as moderate to large as compared with comparator treatments and graded the effects on crucial non-relapse mortality as minor. Based on these considerations, we strongly recommend ruxolitinib as primary treatment in patients with SR-cGVHD.

Response rates are lower in lung and liver GVHD manifestations but relative efficacy of ruxolitinib is preserved. We recommend using ruxolitinib with caution in patients with severe cytopenia or severe uncontrolled infections, considering the side-effect profile of this drug.

For adults with SR-cGVHD, we wanted to assess if belumosudil should be used over additional immunosuppressive agents to ameliorate GVHD severity, reduce non-relapse mortality, or improve failure-free survival. Our evidence review identified a pivotal phase 1/2 trial enrolling 54 patients and the randomised (dose-finding) phase 2 trial enrolling 132 patients.[63,64] The enrolled patients had advanced SR-cGVHD including NIH-defined severe SR-cGVHD in 70% of patients with four or more organs involved in 52% of patients that had received a median of three previous lines of treatment, including ruxolitinib in 21%.[63]

The investigator-assessed best overall response rate of cGVHD was between 62% and 77% in the two studies: the rate was higher than 70% at specific sites (skin, joints, and eyes), but was also clinically relevant for lung involvement (35·9%). Moreover, patient-reported clinically meaningful responses were observed in more than 60% of patients with lung, mouth, eye, or skin involvement.[63,65] The discontinuation rate of belumosudil was 10% in the pooled analysis of the two studies and failure-free survival was 54% at 12 months compared with 45% in the historical control. Treatment failure was rarely (7%) caused by non-relapse mortality. In summary, the restricted body of non-comparative evidence reported encouraging safety and a best overall response rate at year 1, which correlated with patient reported outcomes. We therefore considered belumosudil as a potential therapeutic option in adults with SR-cGvHD. A subgroup consideration was that patients at risk of infection or cytopenia might benefit from the low toxicity profile of belumosudil.[66] Belumosudil is not EMA approved and reimbursement can be challenging depending on the health insurance policies in different countries.

The last recommendation to consider was if adults with SR-cGVHD should receive ibrutinib over additional immunosuppressive agents to ameliorate GVHD severity, reduce non-relapse mortality, or improve failure-free survival. The body of evidence included two prospective non-randomised studies[67–69] and a few retrospective trials.[70,71] Limitations of the evidence were the absence of control groups, a low steroid dose at baseline in some of the studies, and the absence of detailed descriptions of SR-cGVHD severity and organ manifestation in some of the trials.

The best overall response rate of cGVHD was between 67% and 74% in the published data. Non-relapse mortality was heterogeneous and ranged between 5·7% and 15·8%; therefore, no indirect comparisons versus other treatment strategies could be extrapolated for this outcome. Failure-free survival was 67% at year 1 in a Japanese study,[67] and 51% in the USA-based study.[69] Adverse events were a concern in this patient population: grade 3–4 adverse events occurred in 71% of patients in the first treatment year in one trial and discontinuation rates for toxicity were 15·8% and 33% in the prospective studies.[67–69] The pooled fatal adverse events in ibrutinib treated patients in the four studies were 18 of 167 (11%) treated patients. Of note, another retrospective study showed significantly lower response rates and a low failure-free survival of 9% after 2-year follow up.[70] It should be noted that the patient populations studied and the metrics used were different between the controlled trials and the retrospective study.

Taken together, the body of evidence showed low quality because of an absence of comparative study groups and several limitations of the phase 2 trials. In particular, the high reported response rates were biased by the high proportion of steroid-dependent cGVHD (and not SR-cGVHD) patients and by the high proportion of patients with mainly skin or oral mucosae involvement. Moreover, the balance between favourable and unfavourable outcomes was restricted by the high rate of severe adverse events. The expert panel therefore considered ibrutinib as a potential therapeutic option for adults with SR-cGvHD. Due to its side effects profile, ibrutinib should be used with caution in patients with a history of frequent bacterial or fungal infections, need for anticoagulation, diarrhoea, or cardiac comorbidities predisposing to atrial fibrillation. We highlight cost and access issues as resource limitations for implementation, which can be challenging depending on the health insurance policies in different countries.

Discussion

In 2018 and 2019, the EBMT developed recommendations for the management of aGVHD and cGVHD using an evidence and consensus-based approach similar to NCCN.[1] Most recently, the GRADE process has become the standard methodology for developing clinical practice guidelines and has been endorsed by the American

Society of Hematology, British Society for Haematology, LeukemiaNet and several other scientific societies inside and outside the field of haematology. We therefore decided to use the GRADE process for updating and expanding EBMT clinical recommendations. Of note, the GRADE method cannot overcome the limitations of evidence (eg, no comparative studies available), but allows shaping of all the available data in a transparent and synoptic way (eg comparator-specific and outcome-specific), thus enabling the panellists to formulate robust recommendations and the readers and users to understand which pieces of evidence supported the statements.

For the setting of GVHD prophylaxis, we have identified the use of PTCy versus rATG as an important topic needing new recommendations because of improved evidence and the increased use of PTCy. In allogenic HSCT from MUDs and MMUDs, we now consider rATG or PTCy as standard of care for GVHD prophylaxis and we strongly recommend using rATG or PTCy. The possibility of combining both strategies to further increase efficacy is potentially attractive and is currently being tested in clinical practice.[79] Of note, a recent EBMT registry study of patients with acute myeloid leukaemia undergoing MUD allogenic HSCT with PTCy prophylaxis addressed the question of combining PTCy with rATG.[80] In total, 421 transplantation recipients without rATG (PTCy only) were compared with 151 patients with ATG (PTCy plus rATG). There was no difference with respect to aGVHD and cGVHD of all grades, non-relapse mortality, relapse, leukaemia-free survival, overall survival, and GVHD-free and relapse-free survival between the study cohorts. We conclude that the available evidence is not yet sound enough to provide recommendations on combining rATG with PTCy. In allogenic HSCT from MRDs, we found less evidence of a clinical benefit of PTCy use due to the restricted number of studies involving MRD patients and we therefore did not change our previous recommendation to use rATG in MRD transplantations.

On the basis of moderate quality of evidence showing large beneficial effects on aGVHD response rates and failure-free survival,[49–52] we now recommend ruxolitinib as primary treatment for SR-aGVHD irrespective of severity or organ involvement. The reason is that the evidence showed benefit in patients with different types of organ involvement (skin, liver, and gastrointestinal) and different aGVHD severities. SR-aGVHD subgroups for which we consider the use of ruxolitinib more crucial are patients with severe cytopenia and patients with uncontrolled infections. An important and widely open clinical question is which treatment to use in patients with SR-aGVHD not responding to ruxolitinib, with ruxolitinib toxicity, or contraindications. There is low quality of evidence and the best recommendation we can give is to include patients in clinical trials. Current practice beyond second-line treatment is one of the following: alemtuzumab, alpha1-antitripsin, basiliximab, cellular therapies (mesenchymal cells or regulatory T cells) daclizumab, ECP, faecal microbiota transplantation, MMF, methotrexate, pentostatin, rATG, sirolimus, or vedolizumab. Centres should follow their institutional guidelines.

In the setting of SR-cGVHD, there are now three new substances available namely ruxolitinib (FDA and EMA approved), belumosudil, and ibrutinib (both FDA but not EMA approved). Since a randomised trial (REACH 3) and retrospective evidence showed large beneficial effects on SR-cGVHD response rates and failure-free survival,[50–52,61,62] we now recommend ruxolitinib as primary treatment for SR-cGVHD irrespective of severity or organ involvement. Again, this recommendation is based on evidence showing benefit in patients with different types of cGVHD organ involvement and different cGVHD severities. Subgroup considerations are similar to the situation mentioned in aGVHD: patients with severe cytopenia and uncontrolled infections might not be ideal candidates for ruxolitinib because of the side-effect profile of the drug. We have added ibrutinib and belumosudil to the available treatment options for SR-cGVHD. The low toxicity profile and low quality evidence suggesting belumosudil efficacy in patients with SR-cGVHD make it a potentially attractive choice.[63–65] However, there are no solid data justifying a recommendation to generally prefer belumosudil to other available treatment options in SR-cGVHD after ruxolitinib failure or ruxolitinib intolerance and contraindications. Of note, there is an absence of data comparing existing second line SR-cGVHD treatment options. The inclusion of patients in clinical trials is the preferred option when possible. If no inclusion to a clinical trial is possible, the most widely used components beyond second-line treatment for SR-cGVHD currently are: belumosudil (FDA approved), calcineurin inhibitors, ECP, ibrutinib (FDA approved),

Search strategy and selection criteria

References were identified from searches of the Embase database on Nov 30, 2022 (appendix pp 6–9). Five main queries were built to retrieve landmark analyses, randomised clinical trials and meta-analyses, and retrospective or prospective studies reporting graft-versus-host disease (GVHD) therapy or GVHD prophylaxis. The results were restricted to studies written in English and published within the past 10 years. Partially reported studies (abstracts at annual meetings of the American Society of Hematology, European Hematology Association, American Society for Cellular Therapies and Transplantation, or The European Society for Blood and Marrow Transplantation) were included only if reporting comparative studies. The quality of the body of evidence for each outcome was rated according to the GRADE method and rated as high if on the basis of randomised trials or meta-analyses that were not downgraded for indirectness or biases. The quality of the evidence was graded as moderate if the data from randomised trials reported limitations or when evidence was mostly retrieved from non-comparative studies. Evidence was graded as low quality if data from longitudinal studies were not consistent or were indirect. Evidence was graded as very low quality in the case of severe limitations in the available longitudinal studies. Specific queries are detailed in the appendix (p 1).

MMF, mTOR inhibitors, rituximab, pentostatin, proteasome inhibitors, and tyrosine kinase inhibitors. The absorption of oral drugs (eg, ruxolitinib, belumosudil, or ibrutinib) might be reduced in patient with severe malabsorption or diarrhoea.

As future perspectives, we consider the following areas as research priorities: (1) combination therapies as first treatment or salvage treatments of aGVHD and cGVHD (eg, using ECP as combination partner), (2) the use of biomarkers for risk adapted GVHD treatment, (3) evaluating steroid-free regimens (eg, ruxolitinib) as first-line therapies in aGVHD and cGVHD, (4) performing further well designed randomised trials with newer substances as SR-GVHD treatment, and (5) integrating non-pharmacological treatment approaches into clinical trials (eg, physiotherapy).

The EBMT proposes to use the current recommendations as the basis for routine management of GVHD during allogenic HSCT. Our recommendations favour European practice and do not necessarily represent global preferences.

Contributors

All authors contributed substantially to the manuscript. OP and MMa designed the statements, organised the GRADE process, and wrote the manuscript. All other authors were panel members and approved or disapproved the statements at different rounds. All authors critically revised and approved the manuscript. All authors agree that they are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved. No writing assistance other than copy editing was provided.

Declaration of interests

OP received honoraria or travel support from Gilead, Jazz, Merck, Sharp & Dohme (MSD), Novartis, Pfizer, and Therakos; received research support from Incyte and Priothera; and is a member of advisory boards to Equillium Bio, Jazz, Gilead, Novartis, MSD, Omeros, Priothera, Sanofi, Shionogi, and SOBI. FP has received travel support and was member of advisory board of GlaxoSmithKline, Amgen, Roche, and Janssen. HG received honoraria for participation in advisory boards and speakers' bureau from Celgene, Gilead, Novartis, Roche, Sanofi, Takeda, and Therakos. HS reports having received personal fees from Incyte, Janssen, Novartis, Sanofi, and from the Belgian Hematological Society (BHS); reports research grants from Novartis and the BHS; and has received non-financial support (travel grants) from Gilead, Pfizer, the European Society for Blood and Marrow transplantation and the Center for International Bone Marrow Transplantation Research. MAr is on the advisory board of Neovii and reports research support from Therakos and Roche. NK received honoraria from Kite–Gilead, Jazz, MSD, Neovii Biotech, Novartis, Riemser, Pfizer, BMS; and research support from Neovii, Riemser, Novartis and Deutsche Knochenmarksperderdatei. AS has received honoraria from Takeda, Bristol-Myers Squibb–Celgene, MSD, Janssen, Amgen, Novartis, Kite–Gilead, Sanofi, Roche, and Alexion; is a consultant to Takeda, Bristol-Myers Squibb–Celgene, Novartis, Janssen, Gilead, Sanofi; and has received research support from Takeda. FB participated in advisory board meetings and received speaker fees from NEOVII, Sanofi, Takeda, and Novartis. SG received honoraria or travel support from Novartis and Janssen, and is member of advisory boards to Novartis and Janssen. ZP received honoraria from Sanofi and Therakos. DW received a research grant from Novartis, and received honoraria from Novartis, Takeda, Mallinckrodt, Sanofi, Incyte, Behring, and NEOVII.

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