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Practice patterns in chronic graft-versus-host disease patient management and patient reported outcome measures across the EBMT allogeneic transplantation network

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TO THE EDITOR:

BACKGROUND

Chronic graft-versus-host disease (cGvHD) is one of the most common life-threatening complications following allogeneic haematopoietic stem cell transplantation (alloHSCT). Understanding outcome after alloHSCT requires a full evaluation of the patient's health status, including cGvHD and patient reported outcomes (PROs). In an effort to better understand practice patterns across European countries, a survey was initiated by the Integrated European Network on cGvHD (an EU-funded COST Action CA17138 EUROGRAFT, www.gvhd.eu) and the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation (EBMT). This report shares results of the survey, offering a snapshot view of current practice patterns in the context of long-term care of cGvHD patients.

METHODS

Our self-designed 38-item online survey (Supplementary Material) was intended to collect data regarding transplant center characteristics, data registration practices, the use of NIH criteria in clinical routine, biopsies/biomarkers for clinical assessment, cGvHD cell-based therapies, and PROs. The survey used computer adapted testing methods and took ~10 min to complete. All centers participating in the COST Action EUROGRAFT and all EBMT centers performing alloHSCT were invited by email for participation in the survey. Data were collected between July 2019 and July 2020. Appropriate descriptive statistics were used. In case of multiple entries for a single center ($n = 4$), only the entry from the most senior staff member was included for the analysis. Missing data was reported as such.

FINDINGS

Center characteristics

Survey results are summarized in Table 1. A total of 72 centers out of 424 invited centers from 24 countries responded to the survey, representing ~17% of all alloHSCT centers and 19.6% of all transplanted patients within the EBMT network [1]. The majority of participating alloHSCT centers were from Europe with exception of three centers based in Asia and one in Latin America. Survey responses were mainly submitted by physicians and data managers. Of note, the size of the transplant programs differed between responding (mean \pm SD, $n = 47 \pm 40$ transplants/year) vs.

non-responding (mean \pm SD, $n = 39 \pm 31$ transplants/year) centers (Supplementary Material).

Chronic GvHD patient diagnosis and management

Over 80% of respondents reported that post-transplant care was provided by multidisciplinary teams comprised of clinicians including subspecialists such as pulmonologists, gynecologists, ophthalmologists, and dermatologists. The majority of responding centers ($n = 65$; 90.3%) used their own database for collecting and storing patient information. Almost all participating centers ($n = 68$; 94.4%) reported using NIH consensus criteria on cGvHD diagnosis and severity grading, while 51% of responders used NIH response criteria outside of the context of clinical trials. The top three reasons for not using these criteria were their complexity, the lack of suitability for use in children as well as time constraints.

Only a small fraction of centers ($n = 5$; 6.9%) used specific biomarkers (e.g., Reg3-alpha, ST2, CXCL9 etc.) in the context of cGvHD. Collection and storage of patient samples for future assessment of biomarkers was not a common practice either, with less than one third of centers (22/72) collecting patient samples. Approximately 54.2% ($n = 39$) of responding centers reported using cell-based therapies for treatment of cGvHD. Most frequently used therapies were mesenchymal stromal cells (MSCs) ($n = 27$), extracorporeal photopheresis (ECP) closed system ($n = 24$) and ECP open system ($n = 19$). In contrast, cell-based therapies were rarely used in prophylaxis ($n = 4$; 10.2%).

Collection and use of PROs

The collection of PROs in routine practice was limited ($n = 22$; 30.6%). When used, PRO questionnaires were essentially used as an integral part of clinical evaluation and mainly administered to patients using paper and pencil ($n = 19$; 86.4%). Standardized questionnaires or questionnaires developed for specific clinic or research purposes were both used for PRO data acquisition. The most common PRO measures used were the Lee cGvHD symptom scale [2] ($n = 6$), the FACT-BMT ($n = 6$) and the NIH Form B ($n = 5$). Notably, centers reporting use of PROs frequently collaborated with patient associations/support/advocacy groups ($n = 12$; 63.2%). Lack of time and lack of resources were the most common barriers for data collection.

DISCUSSION

With the improvement of transplantation outcome [3] and the growing number of alloHSCT survivors [4], chronic diseases such as cGvHD are becoming a growing concern of healthcare systems. Our survey illustrates the current trends in cGvHD management and use of PROs in alloHSCT centers across the EBMT and COST Action EUROGRAFT network, highlighting a high uptake of NIH criteria in

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Table 1. Summary results of the survey.

Center responses	N (%)
Total centers responding	72 (17.0)
Data registration	
Use own registry outside of EBMT	65 (90.3)
Use of NIH criteria	68 (94.4)
Routinely use NIH criteria for diagnosis and severity grading outside of clinical trials ^a	
NIH2005	13 (19.1)
NIH2014	6 (8.8)
Both	49 (72.1)
Using NIH response criteria outside clinical trials	37 (51.4)
Use of Biomarkers	
Confirming skin, ocular and oral mucosa cGvHD by histopathology:	
Rarely (<10%)	26 (36.1)
Sometimes (10–39%)	16 (22.2)
Often (40–74%)	17 (23.6)
Routinely (>75%)	7 (9.7)
Use of specific biomarkers	5 (6.9)
Collecting and storing patient samples ^a	22 (30.6)
At calendar-driven time points	15
At the onset of cGvHD	10
During the treatment of cGvHD	7
Before transplantation	3
Use of PROs	22 (30.6)
Setting of use of PROs ^a :	
As integral part of the clinical evaluation	20
As part of the outcome analysis	13
As monitoring of response to treatment	13
For referral to specialists	9
Most common reasons for not using PROs ^a :	
Resource constraints	36
Time constraints	33
Not available in the required language	14
Not familiar with interpretation of PRO data	7
Additional burden for the patients	5
Types of questionnaires used ^a	
Standardized	18
Questionnaires developed for specific clinic or research purposes	11
Types of standardized questionnaires used ^a :	
FACT-BMT	6
Lee chronic GvHD symptom scale	6
NIH Form B	5
SF-36	4
EORTC QLQ-C30	3
EQ5D	3
Other	10
Use of cell-based cGvHD therapies ^a	39 (54.2)
MSCs	27
ECP closed system	24
ECP open system	19
Tregs	5

PRO patient reported outcomes, MSC mesenchymal stromal cells, ECP extracorporeal photopheresis, Tregs regulatory T cells.

^aDenotes that several answers were possible.

routine practice, going beyond the initial evaluation of Duarte et al. [5]. Despite recent advances in the field [6], the use of biomarkers and cellular therapies for cGvHD remain modest. Finally, while already 17% of replying centers indicated the use of PRO's in clinical routine, their integration in clinical care should be promoted based on current recommendations indicating their validity in including the patient's perspective in transplantation outcome evaluation [7–9].

CONCLUSIONS

The interpretation of this survey needs to take into account the limited response rate and the risk of a potential responder bias

since information was likely provided mainly by centers with a particular interest in cGvHD and long-term care. In line with this, the observed difference in the size of the transplant programs between responding and non-responding centers may explain, at least in part, reported results of limited use of PROs and biomarkers. Larger and/or more experienced alloHSCT centers may have better infrastructure and resources than centers with smaller transplant programs for real-world implementation of NIH response criteria. Our results might therefore not be fully representative of common practice across Europe. Nevertheless, this survey highlights the need for the harmonization of current cGvHD management practices. This underpins one of the aims of COST Action EuroGraft to expand collaboration between European transplant centers and provide training for transplant programmes to foster a harmonized approach for diagnosis and treatment of cGvHD. This COST Action is offering a new platform to develop common initiatives in cGvHD management to optimize long-term outcome of alloHSCT patients.

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DATA AVAILABILITY

Original data can be shared at request.

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AUTHOR CONTRIBUTIONS

VP wrote the manuscript and analyzed the data, IS analyzed the data, MG designed the survey on biomarker, MI designed the survey on cellular treatment, DP designed the survey on response assessment, ZP provided support to conduct the survey, CP provided support for the distribution via EBMT, EP distributed the survey via EBMT, CK contributed to the manuscript, AD provided funding for the project, HG designed the survey, GB distributed the survey, OP contributed to the manuscript, AS designed survey for psychosocial aspects, AB designed survey for psychosocial aspects, AO designed the survey on response assessment, AL contributed pediatric aspects, PM-G distributed the survey and contributed to the biomarker part, HA contributed to the designs of the survey, HS corrected the manuscript and supervised the survey, DW supervised the project and corrected the manuscript.

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ADDITIONAL INFORMATION

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