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722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Graft-Versus-Host Disease (GvHD) and Steroid-Refractory GvHD after Allogeneic Hematopoietic Stem Cell Transplantation: A Large Real-World EBMT-Based Epidemiology and Treatment Pattern Study

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Introduction: Graft-versus-host disease (GvHD) is a multi-systemic disorder affecting patients who undergo allogenic hematopoietic stem cell transplantation (allo-HSCT) and is associated with considerable morbidity and mortality both in its acute (a) and chronic (c) forms, particularly in patients with steroid-refractory (SR)-GvHD (Flinn AM and Gennery AR. Fac Rev 2023).Given the lack of real-life data on GvHD, this study was conducted using a large European database with the objective to provide evidence on the epidemiology and treatment patterns in patients with aGvHD, cGvHD, and SR-GvHD.
Methods: This retrospective, observational cohort study was conducted between July 1, 2014 and December 31, 2020 in allo-HSCT patients registered to the European Society for Blood and Marrow Transplantation (EBMT) database. Male or female patients aged ≥12 years at index
(≥18 years for SR-GvHD and ruxolitinib [RUX] cohorts) who had received ≥1 allo-HSCT during this study period (January 1, 2017 to July 1, 2019 for SR-GvHD and RUX cohorts) were included in the study population. The EBMT cohort included all allo-HSCT patients, irrespective of GvHD development post-transplant (Tx). The primary objective was to assess the cumulative incidence of aGvHD and cGvHD in patients from the EBMT cohort who met the inclusion criteria. Overall survival of patients up to 60 months was also assessed in the EBMT cohort. The SR-GvHD cohort comprised a sub-selection of GvHD patients

(from selected EBMT centers) who were diagnosed with SR-aGvHD, SR-cGvHD, or both, some receiving RUX as treatment; from the SR-GvHD cohort, a sub-selection of patients who had been treated with RUX for aGvHD and/or cGvHD, irrespective of treatment line, were included in the RUX cohort.
Results:In the EBMT database, 60,140 patients had received an allo-HSCT. Most patients (94.5%) underwent 1 allo-HSCT, the remaining had >1 procedure. The EBMT cohort included a higher proportion of male patients between 50 and 69 years (Table 1). The main indication for allo-HSCT was acute leukemia. At the time of Tx, most patients were in their early disease stage and had unrelated donors(Table 1). The cumulative incidence of aGvHD was 27.9% and 27.6%, 4 months after first and second Tx, respectively. The cumulative incidence of cGvHD was 37.4% and 29.7%, 60 months after first and second Tx, respectively. aGvHD was of grade 2-4 in 27.1% of patients, and the most affected organ was skin (33.6%, grade 2-4: 19.5%) followed by liver (4.0%, grade 2-4: 2.3%) and gut (4.6%, grade 2-4: 2.8%); however, organ involvement was not collected in many patients. The cGvHD was limited (13.6%), extensive (14.7%) or of unknown grade (3.1%). Graft failure occurred in 5.9% of patients. The overall survival of EBMT cohort patients at 60 months was 53.1% with a median follow-up time of 32.9 months. The most frequent cause of death was relapse/progression (30.6%) followed by infection (27.1%) and GvHD (19.1%).
The EBMT registry contains more SR-GvHD patients but only for subset of 292 SR-GvHD patients, additional information was obtained, of which 37 (34.6%) patients were treated with RUX and 70 (65.4%) with other second-line (2L) treatment for SR-aGvHD. For SR-cGvHD, 59 (31.9%) received RUX and 126 (68.1%) other 2L treatment. Baseline characteristics were comparable between SR-GvHD and the EBMT cohort (Table 1). Within SR-GvHD treatment groups, overall, the baseline characteristics were comparable across RUX and other 2L, and consistent with the EBMT and SR-GvHD cohorts. Compared with other 2L treatment, a slightly higher proportion of RUX-treated patients were females in SR-aGvHD cohort and males in SR-cGvHD cohort. While the most common first-line treatment for aGvHD in both RUX and the other group was methylprednisolone, for SR-cGvHD, it was prednisone+cyclosporine in RUX and prednisone in the other group.
Conclusion:This large retrospective real-world evidence study from the EBMT reports on patients with GvHD after allo-HSCT. The cumulative incidence of aGvHD at 4 months post-Tx and cGvHD at 60 months was similar after the first or the second Tx. Though this study provides valuable insights on the epidemiology and treatment patterns of SR-GvHD patients, interpretation of these data is limited due to the small sample size of RUX and other treatment groups compared with the EBMT cohort.

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Table. Patient disposition and baseline characteristics of patients in GvHD and SR-GvHD cohorts

A. Patient disposition from the EBMT Registry		
Patients with allo-HSCT	N=306,222	
Between 2014 and 2020	N=105,048	
EBMT cohort	N=60,140	
SR-GvHD cohort	N=292	
SR-aGvHD	N=100	
SR-cGvHD	N=185	
Both	N=7	
SR-GvHD patients treated with RUX regardless of treatment line	SR-aGvHD (n=73) SR-cGvHD (n=129)	
B. Baseline characteristics		
n (%)	**EBMT cohort N=60,140**	**SR-GvHD N=292**
Male	35,078 (58.3)[a]	157 (53.8)[b]
Age (years) at transplant	12-18: 2,835 (4.7) 18-29: 6,275 (10.4) 30-39: 5,914 (9.8) 40-49: 9,372 (15.6) 50-59: 15,499 (25.8) 60-69: 17,578 (29.2) ≥70: 2,667 (4.4)	18-35: 40 (13.7) 35-50: 87 (29.8) 50-65: 129 (44.2) >65: 36 (12.3)
Diagnosis at transplant		
Acute leukemia	34,717 (57.7)	147 (50.3)
Chronic leukemia	2,809 (4.7)	19 (6.5)
Lymphoma	3,817 (6.3)	23 (7.9)
Plasma cell disorders	165 (0.3)	1 (0.3)
MDS/MPN	15,831 (26.3)	98 (33.6)
Other[c]	2,801 (4.6)	4 (1.4)
Stem-cell source		
Bone marrow	7,966 (13.2)	22 (7.5)
Peripheral blood	51,128 (85.0)	268 (91.8)
Cord blood	1,046 (1.7)	1 (0.3)
Double cord blood	–	1 (0.3)
Donor relation		
Identical sibling	15,675 (26.1)	98 (33.7)
Matched other relative	671 (1.1)	3 (1.0)
Matched unrelated	1,058 (1.8)	–
Mismatched relative[d]	7,612 (12.7)	25 (8.6)
Mismatched unrelated	523 (0.9)	1 (0.3)
Unrelated	34,601 (57.5)	164 (56.4)
Disease stage at transplant[e]		
Advanced stage	18,963 (31.5)	53 (18.9)
Early stage	27,864 (46.3)	185 (65.8)
Intermediate stage	8,801 (14.6)	39 (13.9)
Other/not applicable/missing	4,512 (7.5)	4 (1.4)
GvHD severity in EBMT (N=60140)	aGVHD[f] Grade 1: 9,898 (16.5) Grade 2: 9,784 (16.3) Grade 3: 4,498 (7.5) Grade 4: 1,994 (3.3) Unknown: 1,007 (1.7)	cGvHD[g] Limited: 8,178 (13.6) Extensive: 8,844 (14.7) Unknown: 1,837 (3.1) Not evaluable, OS < 100 days: 1,388 (2.3)

[a]10,549 male recipients female donors (17.8% excluding missing); [b]63 (21.6%) male recipients female donor; [c]Includes bone marrow failure, inherited disorders, histiocytic disorders, auto-immune diseases, hemoglobinopathies (EBMT) and bone marrow failure (SR-GvHD); [d]includes haploidentical donors (defined as having 2 or more mismatch out of 10 from a family-related donor); EBMT cohort, 95.7% (excluding missing) and for the SR-GvHD cohort includes all those in the mismatched relative category, with one SR-aGvHD patient for which the number of HLA mismatch is unknown; [e]Disease stage is defined in the following way: Minor response, relapse, progression, CP1, stable disease, untreated, accelerated phase, blast crisis, PR1, VGPR, nPR or ≥ PR2, Prim Refr/noCR = Advanced stage; CR2, Chronic phase (not specified), CR (not specified), CP2, CP3 or more = Intermediate stage; CR1, CP1 = Early stage; all remaining categories = Other/not applicable/missing; [f]aGvHD grade is based on the maximum grade of aGvHD after first allogeneic transplantation and on aGvHD organ involvement indicators. Based on organ involvement, aGvHD grade is assigned in cases where grade should be higher; [g]cGvHD grade is based on grade after first allogeneic transplantation and maximum grade of cGvHD measured during follow-up, in which the highest grade is chosen.
aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; EBMT, European Society for Blood and Marrow Transplantation; MDS, myelodysplastic syndrome; MPN, Myeloproliferative neoplasms; SR-GvHD, steroid-refractory GvHD

Figure 1

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