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CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Allogeneic Hematopoietic Cell Transplantation in Advanced Systemic Mastocytosis: A retrospective analysis of the DRST and GREM registries

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We identified 71 patients with AdvSM (aggressive SM [ASM], SM with an associated hematologic neoplasm [SM-AHN, e.g., acute myeloid leukemia, SM-AML], mast cell leukemia [MCL]) in two national registries (DRST/GREM) who received an allogeneic hematopoietic cell transplantation (alloHCT) performed in Germany from 1999–2021. Median overall survival (OS) of ASM/SM-AHN ($n = 30$, 45%), SM-AML ($n = 28$, 39%) and MCL ± AHN ($n = 13$, 19%) was 9.0, 3.3 and 0.9 years ($P = 0.007$). Improved median OS was associated with response of SM (17/41, 41%; HR 0.4 [0.2–0.9], $P = 0.035$) and/or of AHN (26/43, 60%, HR 0.3 [0.1–0.7], $P = 0.004$) prior to alloHCT. Adverse predictors for OS included absence of *KIT* D816V (10/61, 16%, HR 2.9 [1.2–6.5], $P < 0.001$) and a complex karyotype (9/60, 15%, HR 4.2 [1.8–10.0], $P = 0.016$). HLA-match, conditioning type or transplantation at centers reporting above-average alloHCTs (≥ 7) had no impact on OS. Taking into account competing events at years 1, 3 and 5, relapse-related mortality and non-relapse mortality rate were 15%/23%, 20%/30% and 23%/35%, respectively. Irrespective of subtype, subsequent treatment response was achieved in 13/30 (43%) patients and was highest on midostaurin/avapritinib (7/9, 78%). We conclude that outcome of alloHCT in AdvSM is more affected by disease phenotype and treatment response prior to transplant than by transplant characteristics.

Leukemia (2024) 38:810–821; <https://doi.org/10.1038/s41375-024-02186-x>

INTRODUCTION

Systemic mastocytosis (SM) is characterized by accumulation of clonal, neoplastic mast cells within the bone marrow and additional organ systems, e.g., skin and gastrointestinal tract [1, 2]. Advanced systemic mastocytosis (AdvSM) comprises aggressive systemic mastocytosis (ASM), SM with an associated hematologic or myeloid neoplasm (SM-AHN/SM-AMN) according to World

Health Classification (WHO)-HAEM5 or International Consensus Classification (ICC), respectively, and mast cell leukemia (MCL) ± AHN as the most aggressive subtype impacting on overall survival (OS) [3, 4]. In >90% of patients, a somatic point mutation in *KIT* at codon 816 (*KIT* D816V) is the primary disease driver [5–7]. In AdvSM, 60–80% of patients harbor additional somatic mutations, some of which confer an adverse impact on prognosis, e.g.,

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Received: 23 December 2023 Accepted: 14 February 2024

Published online: 6 March 2024

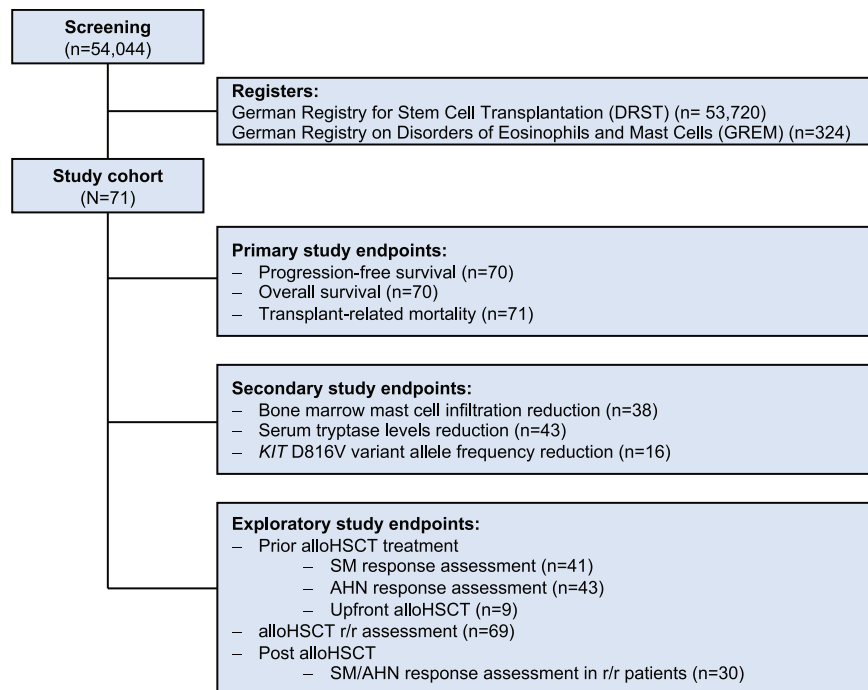


Fig. 1 Study profile. Patients were selected from the ‘German Stem Cell Transplantation Registry’ (DRST) or from the ‘German Registry on Eosinophils and Mast Cells’ (GREM).

mutations in *SRSF2*, *ASXL1*, *RUNX1* (S/A/R gene panel), *EZH2*, *JAK2*, and others [8–12].

In addition to conventional chemotherapy, e.g. to the purine analog cladribine [13–16], the recent development of targeted treatments, e.g. with the multikinase/KIT inhibitor midostaurin [17–21] or the specific KIT D816V inhibitor avapritinib, has substantially extended therapeutic alternatives [22–25]. However, with data from only one larger retrospective analysis on 57 patients available, timing, type of conditioning and post-transplant strategies of allogeneic hematopoietic cell transplantation (alloHCT) as the only curative treatment option remain elusive so far [26]. The advent of reduced intensity conditioning (RIC) [27] and alternate donor sources (e.g. haploidentical alloHCT) [28, 29], have expanded the availability of alloHCT to an increasing number of patients. However, outcome of alloHCT is affected by relapse and non-relapse morbidity and mortality (NRM).

We therefore sought to retrospectively analyze the impact of baseline characteristics, response status and various transplant settings on response, progression-free (PFS) and overall survival (OS) after alloHCT in patients with diagnosis of AdvSM and enrollment within the ‘German Stem Cell Transplantation Registry’ (DRST) or the ‘German Registry on Eosinophils and Mast Cells’ (GREM).

METHODS

Data collection

The study cohort consisted of 71 patients who had undergone alloHCT for AdvSM in 20 German transplant centers between 1999 and 2021 accumulating into a 372 and 211 patient-years overall follow-up period since time of diagnosis and start of alloHCT, respectively. Patient data were collected from the DRST ($n=65$) with additional data from the GREM ($n=6$). Nine patients (8%) were previously reported by Ustun et al. [26]. Data collection from the registries was performed by query of ‘SM + alloHCT’ in June 2022. Eligibility criteria included: (i) diagnosis of ASM, SM-AHN, SM with an acute myeloid leukemia (AML) as subtype of SM-AHN or MCL±AHN according to the WHO-HAEM5 criteria, (ii) alloHCT and (iii) enrollment in either the DRST and/or GREM registry (Fig. 1). Following approval from the respective institutional research boards, we collected

transplant data from MED-A forms, and contacted the participating centers to obtain additional information on patients’ diagnosis, specific parameters of SM, e.g. bone marrow (BM) mast cell (MC) infiltration, serum tryptase level, *KIT* D816V variant allele frequency (VAF), treatment prior to and after alloHCT, and outcome data (response, PFS and OS). Individual information was collected pseudo-anonymously using a data collection form, and transferred to the data collection centers (University Hospitals Aachen and Mannheim). The mastocytosis reference and transplant centers Aachen and Mannheim carried out a post-hoc manual review of the data for identification of inconsistencies and outliers, which were confirmed or revised in collaboration with the reporting center. Classification of conditioning regimes in myeloablative (MAC) or reduced intensity conditioning (RIC) regimes followed proposed definitions based on the duration of cytopenia and need of stem cell support [30]. Informed patient consent was given by all patients via the two registries. The study design adhered to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the Medical Faculties Aachen and Mannheim (Germany).

Study endpoints

Primary study endpoints included PFS and OS defined as time from date of alloHCT to date of progression of the SM and/or the AHN component, death or date of last follow-up (if progression-free) and time from date of alloHCT to death or date of last follow-up (if alive), relapse-related mortality (RRM) and NRM. Secondary endpoints included changes in the BM MC infiltration, serum tryptase levels, and *KIT* D816V VAF. Exploratory endpoints considered type, number of lines and principal investigator-assessed response to treatment prior to and after alloHCT, assessed qualitatively (response vs. non-response), and reviewed by the data collection center. Due to the limitations of retrospective, multicentric data collection, standardized response criteria such as the modified Valent criteria, International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) ECNM criteria or Pure Pathological Response criteria could not be utilized [20, 31–33].

Statistical analysis

Statistical analyses performed on clinical, laboratory and molecular parameters were obtained at the time of diagnosis/first referral to the servicing center and throughout the disease course. Continuous variables were analyzed for statistical differences using the Student’s *t*-test. If the values were not normally distributed, a Wilcoxon rank-sum test was

Table 1. Patient characteristics in different AdvSM subtypes.

	All	ASM/SM-AHN	SM-AML	MCL ± AHN
Number of patients, <i>n</i> (%)	71 (100)	30 (42)	28 (39)	13 (18)
Age in years at Dx; median (range)	58 (21–84)	57 (27–67)	59 (21–84)	51 (27–74)
Age in years at alloHCT; median (range)	59 (21–84)	59 (31–68)	60 (22–84)	55 (28–75)
Male, <i>n</i> (%)	49/71 (69)	21/30 (70)	19/28 (68)	9/13 (68)
Disease characteristics before alloHCT				
Karnofsky performance score ≥90%, <i>n</i> (%)	37/63 (59)	18/27 (67)	12/25 (48)	7/11 (64)
Serum tryptase ≥125 µg/L, <i>n</i> (%)	18/44 (41)	6/16 (38)	6/16 (38)	6/12 (50)
Bone marrow mast cell infiltration ≥20%, <i>n</i> (%)	27/40 (68)	10/17 (59)	7/15 (47)	11/12 (92)
<i>KIT</i> D816V positivity, <i>n</i> (%)	52/62 (84)	22/24 (92)	23/25 (92)	7/13 (54)
<i>SRSF2/ASXL1/RUNX1</i> positivity, <i>n</i> (%)	25/48 (52)	12/19 (63)	11/19 (58)	2/10 (20)
Cytogenetics, aberrant, <i>n</i> (%)	23/62 (37)	5/23 (22)	15/27 (56)	3/12 (25)
Cytogenetics, complex aberrant, <i>n</i> (%)	9/62 (15)	2/23 (9)	4/27 (15)	3/12 (25)
Disease course before alloHCT				
Lines of therapies; median (range)	2 (0–5)	1 (0–4)	2 (0–5)	3.5 (1–5)
Involvement of tyrosine kinase inhibitors, <i>n</i> (%)	35/71 (49)	14/30 (47)	9/28 (32)	12/13 (92)
Involvement of midostaurin/avapritinib, <i>n</i> (%)	27/71 (38)	10/30 (33)	5/27 (19)	11/13 (85)
Years to alloHCT since AdvSM Dx; median (range)	1.2 (0.1–16.7)	1.5 (0.3–16.7)	1.0 (0.0–12.7)	1.2 (0.2–12.7)
Years to alloHCT since AHN/AML Dx; median (range)	1.1 (0.1–16.7)	1.6 (0.2–16.7)	0.3 (0.1–3.1)	1.0 (0.2–12.7)

AHN associated hematologic neoplasm; alloHCT allogeneic hematopoietic stem-cell transplantation, ASM aggressive systemic mastocytosis, Dx diagnosis, *n* number, SM-AHN systemic mastocytosis with an associated hematologic neoplasm, SM-AML systemic mastocytosis with an acute myeloid leukemia, MCL ± AHN mast cell leukemia with/without an associated hematologic neoplasm.

employed. For categorical variables, Fisher's exact test was used. For the estimation of hazard ratios (HRs) and multivariable analyses, the cox proportional hazard regression model was used. Only variables that demonstrated statistical significance in univariate analyses were incorporated into the multivariable model. Survival probabilities (PFS and OS) were calculated by the Kaplan-Meier Method and compared by the log-rank test. The proportional hazards assumption was tested by the correlation of scaled Schoenfeld residuals with time. The cumulative incidence function was used to account for the presence of competing risks (RRM vs. NRM). In this hypothesis-driven, retrospective data set, analyses were not specifically powered for direct comparisons. In general, a test result with *P* less than .05 was considered as statistically significant. Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), SPSS version 29.0.1 (IBM Corporation, Armonk, NY) and GraphPad Prism version 10.1.1 software (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Patient characteristics

At time of alloHCT, the median patient age was 59 years (range 21–84), with the majority of patients (49/71, 69%) being male. The median time between diagnosis of AdvSM and alloHCT was 1.2 (range 0.1–16.7) years. The Karnofsky performance score at time of alloHCT was ≥90% in 37/63 (59%) patients. The most common subtype close to alloHCT was ASM/SM-AHN in 30/71 (42%; ASM, *n* = 4, 6%; SM-AHN, *n* = 26, 37%), followed by SM-AML (Table S1) in 28/71 (39%, 18/28 [64%] with secondary AML) and MCL ± AHN (Table S2) in 13/71 (18%, 3/13 [23%] with secondary MCL). Diagnoses of (secondary) AML and MCL were mutually exclusive.

The detailed clinical characteristics of the various cohorts are reported in Table 1. Differences included significantly higher levels of BM MC infiltration (median 80% [range 30–100], *P* < 0.001) and numerically higher serum tryptase levels (median 429 µg/L [range 61–2660], *P* = 0.076) in MCL ± AHN while the relative frequency of the *KIT* D816V mutation (7/13, 54%, *P* < 0.001; Table S3) and of additional somatic mutations in *S/A/R* (2/10, 20%, *P* = 0.023) was significantly lower. The presence of an aberrant karyotype [23/62,

37%, including 2 patients with a t(8;21)(q22;q22)] was clustered in SM-AML (15/27, 56%, *P* = 0.008).

An upfront alloHCT (median time between AdvSM diagnosis and alloHCT 1.4 years, range 0.1–3.7) without prior SM- or AHN-directed treatment was performed in 9/71 (13%) patients (Table S4). All other patients received a median of 2 (range 1–5) treatment lines prior to alloHCT. Tyrosine kinase inhibitors (TKI) including midostaurin and avapritinib were less frequently used in SM-AML (9/28, 32%) than in ASM/SM-AHN (14/30, 47%, *P* = 0.259) or MCL ± AHN (12/13, 92%, *P* = 0.005) (Table 1).

Transplant characteristics

Peripheral blood was used as graft source in 67/71 (94%), BM in 4/71 (6%) patients. Detailed donor information was available in 62/71 (87%) patients: 17 (27%) patients received a graft from an HLA-matched (10/10) related donor, 1 (2%) an HLA-mismatched related graft, 25 (40%) an HLA-matched (10/10) unrelated, 12 (19%) an HLA-mismatched unrelated, and 7 (11%) a related haploidentical graft. Overall, 24 different conditioning regimens were utilized with myeloablative conditioning accounting for 43/69 (62%) and reduced-intensity conditioning for 26/69 (38%) patients (Table S5). The most frequently administered conditioning regime consisted of fludarabine and treosulfan or fludarabine and TBI (each 9/68, 13%), followed by busulfan and cyclophosphamide (7/68, 10%).

Total body irradiation as part of the conditioning regimen, varying between 2 and 12 Gy (≥ 8 Gy, 11/17, 65%), was included in 17/69 (25%) patients (Table S6). The median time to neutrophil engraftment (≥ 0.5/nL) was 18 days (range 1–57). Primary graft failure was reported in two patients. Data about chimerism were available in 43/71 (61%) patients. Complete donor chimerism was achieved in 36/43 (84%) patients. Acute (grade I to IV) and chronic (mild to severe) GvHD occurred in 34/67 (51%) and 16/52 (31%) patients, respectively (Table 2).

Transplant outcome

For the entire cohort, the median time of follow-up was 1.4 years (range 0–20.4). PFS and OS for all patients were 52% (standard

Table 2. Transplant characteristics in different AdvSM subtypes.

	All	ASM/SM-AHN	SM-AML	MCL ± AHN
Number of patients, <i>n</i> (%)	71 (100)	30 (42)	28 (39)	13 (19)
<i>Transplant</i>				
<i>Graft source</i>				
PBSC, <i>n</i> (%)	67/71 (94)	29/30 (97)	26/28 (93)	10/13 (92)
BM, <i>n</i> (%)	4/71 (6)	1/30 (3)	2/28 (7)	1/13 (8)
<i>Conditioning</i>				
Myeloablative, <i>n</i> (%)	43/69 (62)	16/28 (57)	16/28 (57)	11/13 (85)
Reduced intensity, <i>n</i> (%)	26/69 (38)	12/28 (43)	12/28 (43)	2/13 (15)
Total body irradiation, <i>n</i> (%)	17/70 (24)	5/29 (17)	6/28 (21)	6/28 (21)
≥8 Gy, <i>n</i> (%)	11/17 (65)	3/29 (10)	4/6 (67)	2/28 (7)
<i>Donor</i>				
MUD, <i>n</i> (%)	25/62 (43)	12/26 (46)	11/24 (46)	2/12 (17)
MMUD, <i>n</i> (%)	12/62 (19)	2/26 (8)	7/24 (29)	3/12 (25)
MRD, <i>n</i> (%)	17/62 (27)	9/26 (35)	3/24 (13)	5/12 (42)
MMRD, <i>n</i> (%)	1/62 (2)	0/26 (0)	1/24 (4)	0/12 (0)
Haploidentical, <i>n</i> (%)	7/62 (11)	3/26 (12)	2/24 (8)	2/12 (17)
Recipient-donor sex mismatched, <i>n</i> (%)	27/66 (41)	13/28 (46)	11/26 (42)	3/12 (25)
Donor age in years at alloHCT; median (range)	33 (17–63)	33 (19–62)	35 (22–63)	48 (17–59)
<i>Graft versus host disease</i>				
<i>Acute graft versus host disease</i>				
I, <i>n</i> (%)	12/67 (18)	7/28 (25)	2/27 (7)	3/13 (23)
II, <i>n</i> (%)	10/67 (15)	5/28 (18)	2/27 (7)	3/13 (23)
III, <i>n</i> (%)	8/67 (12)	3/28 (11)	3/27 (10)	1/13 (8)
IV, <i>n</i> (%)	4/67 (6)	1/28 (4)	2/27 (7)	2/13 (15)
<i>Chronic graft versus host disease</i>				
None, <i>n</i> (%)	36/52 (69)	13/22 (59)	12/19 (63)	11/11 (100)
Limited, <i>n</i> (%)	13/52 (25)	8/22 (36)	5/19 (26)	0/11 (0)
Extensive, <i>n</i> (%)	3/52 (6)	1/22 (5)	2/19 (11)	0/11 (0)
<i>Prophylaxis</i>				
Methorexate, <i>n</i> (%)	24/68 (35)	12/28 (43)	7/27 (27)	5/13 (36)
Cyclosporine, <i>n</i> (%)	58/68 (85)	24/28 (86)	25/27 (93)	9/13 (69)
Tacrolimus, <i>n</i> (%)	10/68 (15)	5/28 (18)	2/27 (7)	3/13 (23)
Mycofenolat mofetil, <i>n</i> (%)		16/28 (57)	15/27 (56)	6/13 (46)

AHN associated hematologic neoplasm, alloHCT allogeneic hematopoietic stem-cell transplantation, AML acute myeloid leukemia, ASM aggressive systemic mastocytosis, BM bone marrow, MCL ± AHN mast cell leukemia with/without an associated hematologic neoplasm, MMRD HLA-mismatched related donor, MMUD HLA-mismatched unrelated donors, MUD HLA-matched unrelated donor, MRD HLA-matched related donor, PBSC peripheral blood stem cell, SM-AHN systemic mastocytosis with an associated hematologic neoplasm.

deviation [SD] ± 6.1%) and 62% (SD ± 5.9%) at 1 year, and 39% (SD ± 6.3%) and 50% (SD ± 6.2%) at 3 years, respectively. Primary diagnosis of ASM/SM-AHN vs. SM-AML vs. MCL ± AHN delineated a three-tier risk stratification (median PFS, 4.5 vs. 0.7 vs. 0.3 years, $P < 0.001$, Fig. 2A; median OS, 9.0 vs. 3.3 vs. 0.9 years, $P = 0.007$, Fig. 2B). Median relative decreases in BM MC infiltration (−79% [range −100 to +233]), serum tryptase levels (−78% [range −99 to +385]) and *KIT* D816V VAF (−100% [range −100 to +10]) prior to post-alloHCT were not statistically different between the three subgroups (Fig. 3).

Taking into account competing events at years 1, 3, and 5, the RRM and the NRM rate was 15%/23%, 20%/30% and 23%/35%, respectively. Reasons for NRM included infections, GvHD, organ toxicity (cardiotoxicity) and combinations/not further specified in 8/22 (36%), 1/22 (5%), 1/22 (5%) and 11/22 (50%) patients, respectively. No statistical differences were observed in RRM ($P = 0.400$) and NRM ($P = 0.200$) based on the subtype of AdvSM (Fig. 2C, Table S7).

Predictors of transplant outcome

Univariate analysis revealed that PFS after alloHCT was adversely impacted by diagnosis of MCL ± AHN (HR 3.5 [95% CI 1.7–7.5], $P < 0.001$), absence of a *KIT* D816V mutation (HR 2.5 [95% CI 1.2–5.4], $P = 0.021$), presence of a complex karyotype (HR 3.0 [95% CI 1.4–6.6], $P = 0.006$) and absence of the use of TKI prior to alloHCT (HR 0.5 [95% CI 0.2–0.9], $P = 0.014$). Multivariable analysis revealed the absence of the use of TKI prior to alloHCT (HR 2.8 [95% CI 1.3–5.9], $P = 0.007$) and a complex karyotype (HR 3.3 [95% CI 1.5–7.2], $P = 0.004$) as independent predictors for PFS.

An adverse impact on OS was unveiled by univariate analyses upon lack of response on SM (response in 17/41, 41%; median OS 4.6 vs. 1.1 years; HR 2.5 [95% CI 1.1–6.0], $P = 0.035$) or AHN (response in 26/43, 60%, median OS not reached vs. 0.4 years; HR 0.302 [95% CI 0.132–0.687], $P = 0.004$) prior to alloHCT (Fig. 4). Transplant-associated OS was further adversely associated by the absence of a *KIT* D816V mutation (HR 2.8 [95% CI 1.2–6.5],

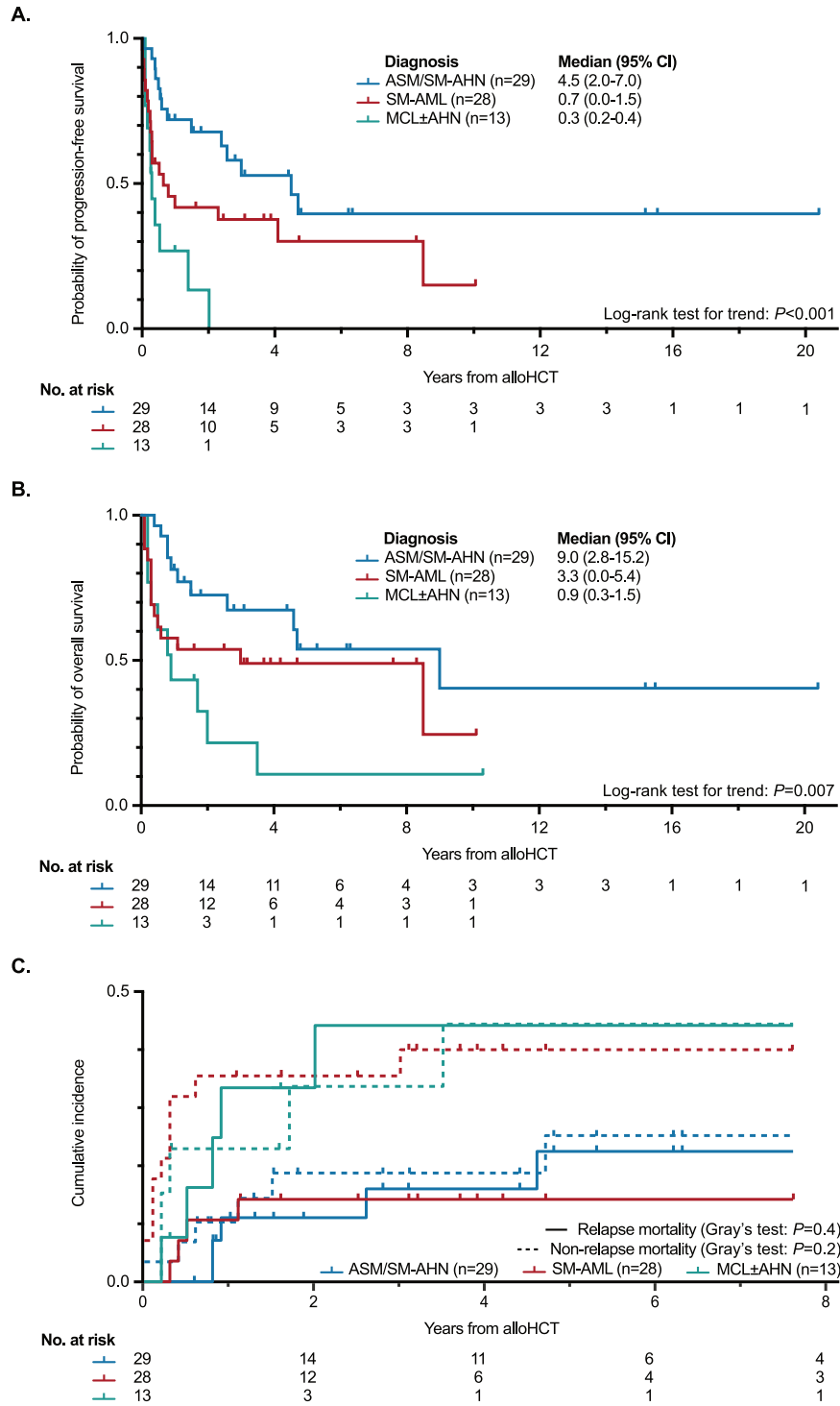


Fig. 2 Survival outcomes. **A** Kaplan–Meier estimates of progression-free survival (PFS) and **B** overall survival (OS) depending on their most advanced disease subtype prior allogeneic stem cell transplantation (alloHCT). **C** Cumulative incidence function of relapse-related mortality and non-relapse mortality. ASM aggressive systemic mastocytosis, MCL±AHN mast cell leukemia with/without an associated hematologic neoplasm, SM-AHN systemic mastocytosis with an associated hematologic neoplasm, SM-AML systemic mastocytosis with an acute myeloid leukemia.

$P = 0.016$) and a complex karyotype (HR 4.2 [95% CI 1.8–10.0], $P = 0.001$). Multivariable analysis revealed the lack of AHN response prior to alloHCT (HR 4.082 [95% CI 1.7–9.8], $P = 0.002$) and a complex karyotype (HR 8.0 [95% CI 2.3–27.1], $P = 0.016$) as independent adverse prognostic factors for OS.

HLA-matching (complete vs. incomplete), type of conditioning (myeloablative vs. dose-reduced intensity), the use of total body irradiation (≥ 8 Gy yes vs. no), transplantation at a center with an above-average number of alloHCT in AdvSM patients (center performed and reported ≥ 7 alloHCTs for AdvSM yes vs. no) or a

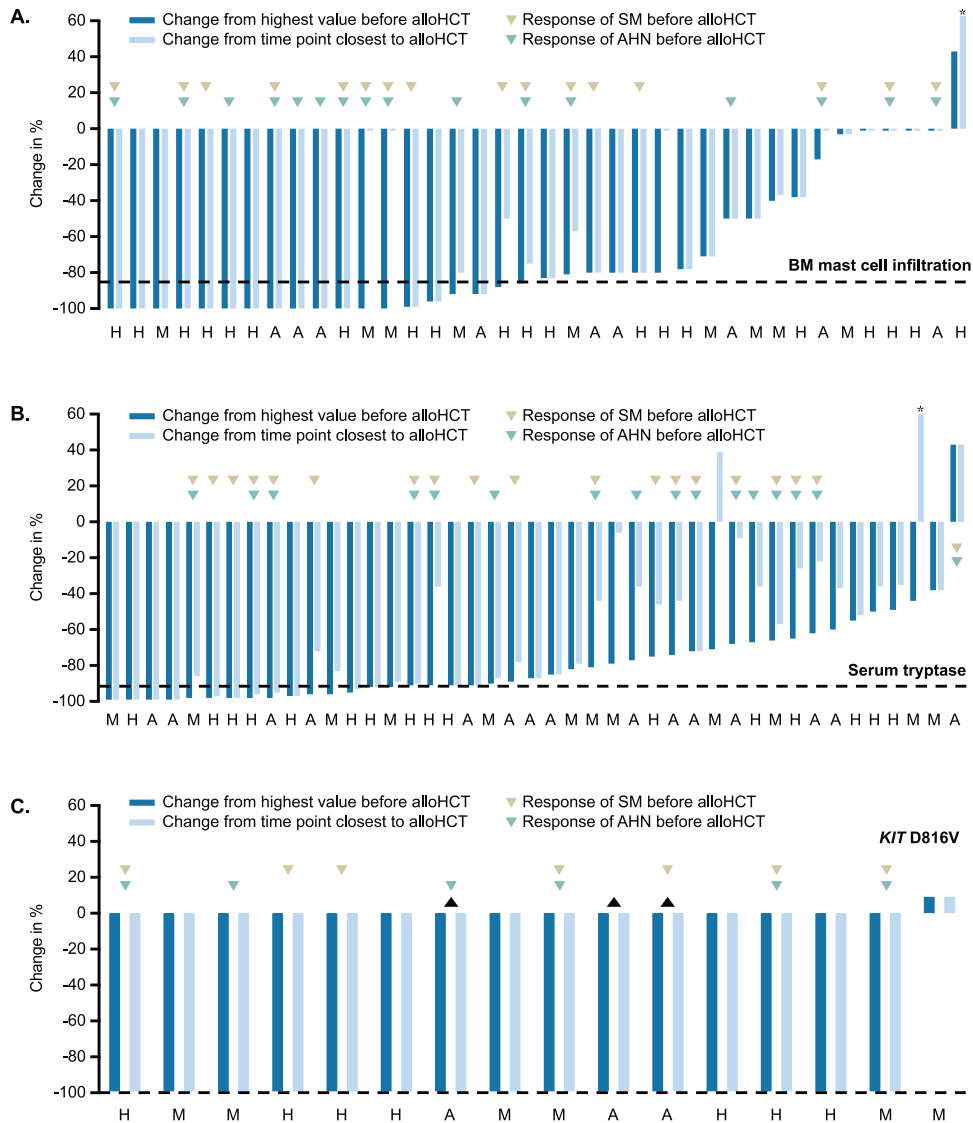


Fig. 3 Response assessment. Waterfall plots of **A** bone marrow (BM) mast cell infiltration, **B** serum tryptase and **C** KIT D816V variant allele frequency in all available patients (relative changes prior to post alloHCT). A systemic mastocytosis with an acute myeloid leukemia, alloHCT allogeneic stem cell transplantation, AHN associated hematologic neoplasm, H systemic mastocytosis with/without an associated hematologic neoplasm (except AML), M mast cell leukemia with/without an associated hematologic neoplasm, SM systemic mastocytosis.

transplantation in the year 2010 or later (Table S8) were not associated with differences in PFS or OS (Table 3).

Posttransplant treatment

During or after alloHCT, 30/71 (42%) patients showed either refractory (9/30, 30%) or relapsed (21/30, 70%; r/r) disease which was highest in MCL ± AHN (11/13, 85%) vs. ASM/SM-AHN (9/30, 30%) and SM-AML (10/28, 36%; $P = 0.002$). Primary refractory disease was predominantly observed in MCL ± AHN (8/9, 89%) vs. SM-AML (1/9, 11%) and ASM/SM-AHN, 0/9, 0%; ($P < 0.001$). The median time to relapse was 0.6 years (range 0.1–4.5) which was more frequent in ASM/SM-AHN (9/21, 43%) and SM-AML (9/21, 43%) vs. MCL ± AHN (3/21, 14%). Considering the two disease components, r/r SM was predominantly observed in MCL ± AHN (10/11, 91%), r/r AHN was higher in SM-AML (6/10, 60%) and ASM/SM-AHN (5/9, 56%).

Overall, 52 treatment lines have been applied in the r/r setting post-alloHCT with a median number of 2 (range 0–4) lines per individual patient. At least one treatment line was applied in 24/30 (80%) patients. Midostaurin/avapritinib, cladribine or other cytoreductive therapies were used in 9/30 (30%), 3/30 (10%) and 14/30

(47%) patients, respectively (Table 4). Donor lymphocyte infusions were applied in 18/30 (60%) patients (ASM/SM-AHN, 7/9, 78%; SM-AML, 7/10, 70%, MCL ± AHN, 4/11, 36%) while a second alloHCT was performed in 2/30 (7%) patients (both SM-AML). A response to treatment regimens after alloHCT was achieved in 13/30 (43%) patients (ASM/SM-AHN, 3/9, 33%, SM-AML, 5/10, 50%; MCL ± AHN, 5/11, 45%) and was highest in 9 patients receiving midostaurin and/or avapritinib (7/9, 78%).

DISCUSSION

Despite the availability and efficacy of KIT targeted therapies, alloHCT remains the only curative treatment option for patients with AdvSM. Our data show that primary disease phenotype, karyotype and endpoints assessed during follow-up such as level of response as well as primary or secondary resistance are critical for outcome of subsequently performed alloHCT. So far, a retrospective multicenter analysis from 2014 including 57 patients (transplanted between 1990 and 2013) represents the only available data collection demonstrating a potential curative

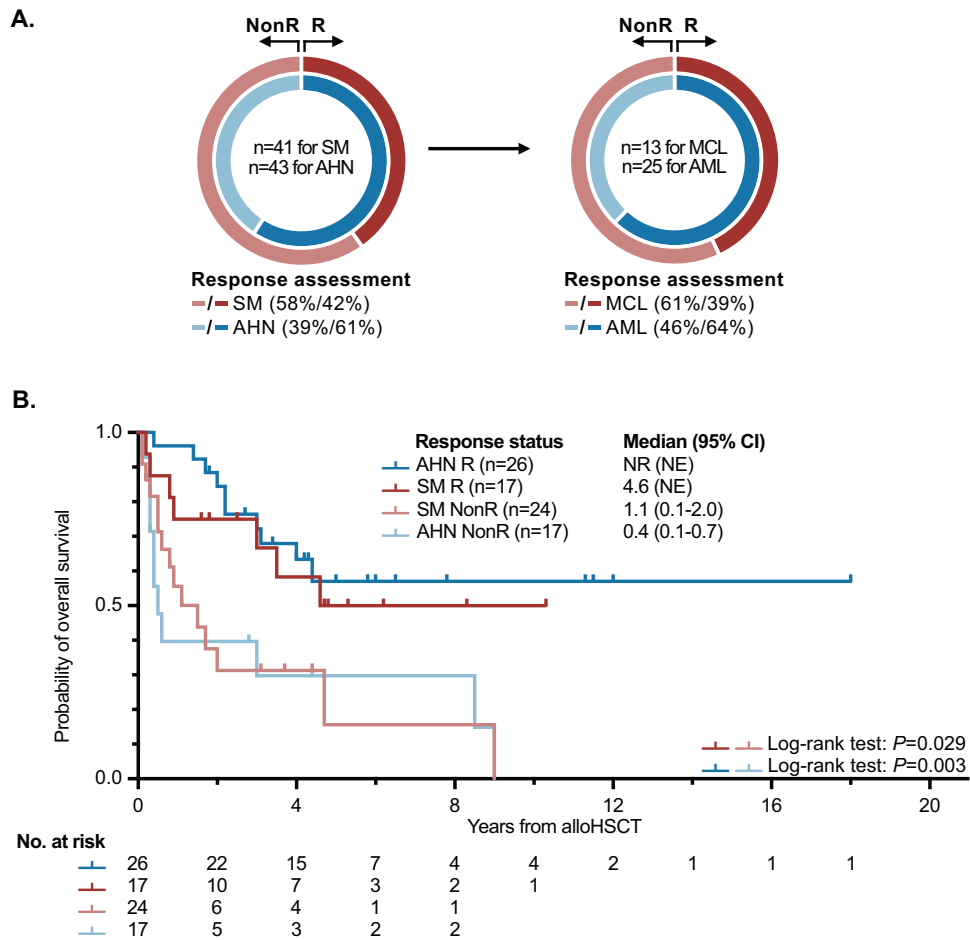


Fig. 4 Survival outcomes based on response assessment. **A** Response status (investigator-assessed) prior to allogeneic stem cell transplantation (alloHCT) regarding the systemic mastocytosis (SM) and associated hematologic neoplasm (AHN) compartment. **B** Kaplan–Meier estimates of overall survival (OS) depending on response status prior to alloHCT. AML acute myeloid leukemia, MCL mast cell leukemia, NonR nonresponse, R response.

benefit of alloHCT in AdvSM [26]. Applying these reported findings into current clinical practice remains however challenging given the increasing complex molecular landscape of AdvSM, the efficacy of KIT inhibitors such as midostaurin and avapritinib, and the continuous developments of transplant procedures, GvHD prophylaxis and supportive care strategies [18–20, 22–25, 34]. A prospective clinical trial in order to assess the best alloHCT strategy will most likely not be performed given the rarity and heterogeneity of AdvSM. Ongoing clinical trials of new KIT inhibitors such as bezuclastinib (NCT04996875) or elenestinib (NCT05609942) pose additional potential challenges on the evaluation of optimal alloHCT integration into the overall treatment concepts. However, in order to address some of the actual questions in regard to alloHCT in AdvSM patients we performed an updated retrospective multicenter study on 71 AdvSM patients who underwent alloHCT in Germany between 1999 and 2021 with 89% of patients transplanted after 2010.

As expected, substantial disparities were noted between the various AdvSM subtypes with a median OS of approximately 1 and 3 years observed in MCL±AHN and SM-AML, respectively. The most inherent characteristics contributing to this unfavorable prognosis include the absence of *KIT* D816V in approximately 50% of MCL patients and the presence of an aberrant karyotype in 56% or a complex karyotype in 15% of patients with SM-AML. Surprisingly, PFS/OS was not adversely affected by established high-risk mutations (HRM) such as *SRSF2*, *ASXL1* or *RUNX1* [8, 10, 11, 18, 34, 35]. In ASM/SM-AHN patients, a median OS of nine years was seen after exclusion of

MCL and AML. These data clearly indicates that alloHCT can overcome poor prognosis conferred by HRM in *KIT* D816V positive AdvSM at least if MCL or AML are absent.

Similar to AML [36–38] or ALL [39], response of the SM and/or the AHN compartment to treatment prior alloHCT significantly prolonged transplant-associated OS. Our data also show that for patients with resistant or progressive disease before alloHCT, this procedure might not be a reasonable rescue option as the graft-versus-AdvSM effect does not seem to be sufficiently effective in patients with high disease burden, a phenomenon known from other myeloid neoplasms [40–42]. To optimize outcome in AdvSM, transplant eligible patients should therefore be transplanted at time of best response to pre-allo treatment; hence, close interdisciplinary cooperation between mastocytosis and transplant centers is warranted to define these time points. The use of tyrosine kinase inhibitors such as midostaurin or avapritinib prior to alloHCT was significantly associated with improved PFS. The use of 24 different conditioning regimens in 71 AdvSM patients demonstrates the lack of a standardized approach for AdvSM patients despite consensus opinions [43, 44]. This inconsistency becomes even more impressive when we consider that all transplantations have been conducted within one country.

Even after adjusting for pre-alloHCT treatment responses (data not shown), updated analyses could not confirm the previously reported superiority of myeloablative conditioning over reduced intensity regimens in terms of PFS [26]. This again highlights the fact, that other parameters such as pre-alloHCT response seem to be more important

Table 3. Factors associated with impacted/improved overall survival and progression-free survival.

Factors	n	Overall survival			Progression-free survival		
		HR (95% CI)	P	n	HR (95% CI)	P	
Demographics							
Age (years) < 60 vs. ≥ 60	70	1.1 (0.6–2.1)	0.768	70	1.2 (0.7–2.1)	0.589	
Sex male vs. female	70	1.3 (0.7–2.7)	0.434	70	1.2 (0.6–2.3)	0.623	
Karnofsky index ≤90% vs. >90%	70	1.4 (0.7–2.8)	0.363	70	1.3 (0.7–2.4)	0.437	
Diagnosis before alloHCT							
Diagnosis of MCL ± AHN yes vs. no	70	2.0 (0.9–4.4)	0.088	70	3.5 (1.7–7.5)	<0.001	
Diagnosis of AML yes vs. no	70	1.4 (0.7–2.7)	0.309	70	1.3 (0.7–2.3)	0.401	
Cytogenetics							
Aberrant yes vs. no	60	1.6 (0.8–3.3)	0.188	60	1.6 (0.8–3.1)	0.156	
Complex aberrant yes vs. no	60	4.2 (1.8–10.0)	0.001	60	3.0 (1.4–6.6)	0.006	
Mutations							
Absence of KIT D816V yes vs. no (or unknown)	61	2.8 (1.2–6.5)	0.016	61	2.5 (1.2–5.4)	0.021	
Presence of S/A/R yes vs. no	47	0.8 (0.4–1.7)	0.599	56	0.6 (0.3–1.2)	0.146	
≥3 additional somatic mutations yes vs. no	56	1.3 (0.6–2.8)	0.432	56	1.0 (0.5–2.1)	0.904	
Treatment before alloHCT							
With tyrosine kinase inhibitors yes vs. no	70	0.6 (0.3–1.1)	0.091	70	0.5 (0.2–0.9)	0.014	
Response status before alloHCT^a							
For SM yes vs. no	41	0.4 (0.2–0.9)	0.035	41	0.6 (0.3–1.2)	0.143	
For AHN including AML yes vs. no	43	0.3 (0.1–0.7)	0.004	43	0.5 (0.2–1.0)	0.067	
Time to alloHCT							
From SM (years) ≥1 vs. <1	70	1.0 (0.5–1.9)	0.946	70	0.8 (0.4–1.4)	0.377	
From AHN (years) ≥1 vs. <1	70	1.5 (0.7–3.0)	0.297	70	1.4 (0.7–2.6)	0.332	
Biomarkers at alloHCT							
Tryptase (µg/L) ≥100 vs. <100	50	0.9 (0.4–1.9)	0.748	50	1.0 (0.5–2.1)	0.928	
Mast cell infiltration (%) ≥25 vs. <25	53	1.3 (0.6–2.7)	0.468	53	1.7 (0.9–3.4)	0.123	
Transplantation							
Conditioning Reduced intensity vs. myeloablative	69	0.9 (0.5–1.8)	0.871	69	0.9 (0.5–1.7)	0.802	
Total body irradiation ≥ 8 Gy yes vs. no	17	0.9 (0.2–3.1)	0.807	17	0.7 (0.2–2.1)	0.480	
HLA match 10/10 vs. others	62	1.2 (0.6–2.5)	0.571	62	1.2 (0.6–2.4)	0.527	
alloHCT before 2009 yes vs. no	70	1.1 (0.4–3.1)	0.799	70	1.3 (0.5–3.5)	0.545	
alloHCT at a center with above-average numbers of alloHCT in AdvSM ^b yes vs. no	70	1.0 (0.5–2.0)	0.964	70	1.1 (0.6–2.0)	0.802	
Full donor chimerism (≥95% donor signal within 30 days) yes vs. no	43	0.5 (0.1–1.9)	0.136	43	0.2 (0.1–1.6)	0.051	

alloHCT allogeneic stem cell transplantation, AHN associated hematologic neoplasm, AML acute myeloid leukemia, MCL ± AHN mast cell leukemia with/without an associated hematologic neoplasm, S/A/R, SRSF2/ASXL1/RUNX1; SM systemic mastocytosis.

^an = 9 patients with upfront alloHCT without any induction therapy were excluded from this analysis.

^bCenter performed and reported ≥7 alloHCT.

Significant results are highlighted in bold.

Table 4. Post-alloHCT treatment in patients with refractory/relapse disease.

	All	ASM/SM-AHN	SM-AML	MCL ± AHN
Number of patients, n (%)	30/71 (42)	9/30 (30)	10/28 (36)	11/13 (85)
Refractory disease, n (%)	9/30 (30)	0/9 (0)	1/10 (10)	8/11 (73)
SM, n (%)	8/9 (89)	–	0/1 (0)	8/8 (100)
AHN, n (%)	0/9 (0)	–	0/1 (0)	0/8 (0)
SM + AHN, n (%)	1/9 (11)	–	1/1 (100)	0/8 (0)
Relapse disease, n (%)	21/30 (70)	9/9 (100)	9/10 (90)	3/11 (27)
SM, n (%)	8/21 (38)	4/9 (44)	2/9 (22)	2/3 (67)
AHN, n (%)	12/21 (57)	5/9 (56)	6/9 (67)	1/3 (33)
SM + AHN, n (%)	1/21 (5)	0/9 (0)	1/10 (10)	0/3 (0)
Years to relapse, median (range)	0.6 (0.1–4.5)	0.6 (0.3–4.5)	0.4 (0.1–4.1)	1 (0.4–1.4)
Post-alloHCT treatment	n (%)	Response, n (%)	n (%)	Response, n (%)
Lines of therapy, median (range)	2 (0–4)	–	2 (0–4)	–
Tyrosine kinase inhibitors				
Midostaurin	8/30 (27)	4/8 (50)	2/10 (20)	5/11 (45)
Avapritinib	4/30 (13)	3/4 (75)	0/10 (0)	4/11 (36)
Other TKI ^a	3/30 (10)	0/3 (0)	1/10 (10)	1/11 (9)
Cytoreductive therapy				
Cladribine	3/30 (10)	0/3 (0)	1/10 (10)	1/11 (9)
Others ^b	14/30 (47)	5/14 (36)	5/10 (50)	4/11 (36)
Donor lymphocyte infusion	18/30 (60)	5/18 (28)	7/10 (70)	4/11 (36)
Second alloHCT	2/30 (7)	2/2 (100)	2/10 (20)	0/11
Response to post-alloHCT treatment^c				
Response, n (%)	13/30 (43)	3/9 (33)	5/10 (50)	5/11 (45)
No response or progression, n (%)	10/30 (33)	3/9 (33)	3/10 (30)	4/11 (36)

alloHCT allogeneic stem cell transplantation, ASM aggressive systemic mastocytosis, DLJ donor lymphocyte infusion, MCL ± AHN mast cell leukemia with/without an associated hematologic neoplasm, r/r relapsed/refractory, SM-AHN systemic mastocytosis with an associated hematologic neoplasm, TK tyrosine kinase inhibitor.

^adasatinib, imatinib, nilotinib.

^bazacitidine, bortezomib, decitabine, hydroxyurea, induction chemotherapy, nivolumab, venetoclax.

^cOverall response independent of response in either the SM and/or the AHN compartment.

than conditioning intensity. Therefore, future strategies for older or more fragile patients should prioritize achieving an optimal treatment response before considering alloHCT to employ reduced-intensity conditioning regimens successfully.

Posttransplant treatment was exclusively used in patients with r/r disease status. As expected, the relative frequency of r/r patients with 85% was highest in patients with MCL ± AHN with most of these patients (62%) already suffering from refractory disease prior to alloHCT. As pointed out before, the use of myeloablative conditioning was insufficient to overcome this mast cell resistance. While in approximately 50% of patients with r/r MCL ± AHN, a partial response was achieved on midostaurin ($n = 1$), DLI ($n = 1$) or avapritinib ($n = 3$), future strategies might focus on maintenance therapy or measurable residual disease-based pre-emptive approaches using effective TKIs, e.g. similar to strategies used in AML patients with FLT3 mutation [45].

A major limitation of this analysis is insufficient information on post-transplant quantification of residual disease including BM MC infiltration (24/71, 34%), serum tryptase levels (33/71, 47%) and *KIT* D816V VAF (48/71, 68%) not being available in a significant number of patients. This lack of data - even as chimerism analyses on BM aspirates were regularly performed - was particular predominant in patients in which the AHN compartment was the primary driver for the alloHCT concept, e.g. SM-AML [6, 9, 18]. In consequence, residual MC disease may be inadvertently overlooked during follow-up. The lack of attention in regard to the MC component post-alloHCT could be a significant disadvantage especially given the availability of potent MC-directed treatment options such as midostaurin and avapritinib [18–20, 46–49].

Similarities and differences between the cohort reported by Ustun et al. and the current cohort are at least partly related to changes in the real-world practice of alloHCT over a 10-years period between the two reports. For example, direct comparisons across the various subtypes were not possible because advanced morphologic and genetic characterization conferred into a higher relative frequency of AHN (87% vs. 67%) in the current cohort. Moreover, the number of cases allowed the separation of SM-AML from SM-AHN because it is characterized by an inherent disease phenotype and different clinical trajectory. In the current cohort, patients were older (median age 59 vs. 46 years) and the relative frequencies of unrelated (60% vs. 31%) or haploidentical donors (11% vs. 2%) were higher while the relative frequencies on the use of MAC regimens (62% vs. 63%) and TBI (24% vs. 28%) were similar. Rates of NRM were 23% (based on cumulative incidence function) and 20% after 1 year and the subtype-independent OS was approximately 60% and 50% after 1 and 3 years in both cohorts. In this respect, it should be emphasized that the poor prognosis of MCL (with or without AHN) has not markedly improved over the last decade.

In conclusion, alloHCT can confer long-term PFS/OS in patients with AdvSM, especially when alloHCT will be performed at time of optimal response. To achieve the maximum benefit from pre- and post-allogeneic strategies and from the transplant itself, collaborative efforts between mastocytosis experts and transplant centers are essential. Adequate monitoring of residual disease could provide valuable guidance for the pre-emptive use of KIT inhibitors post-transplant. The rapidly evolving landscape of AdvSM treatment necessitates continuous adaptation in integrating alloHCT into patient care. To facilitate upcoming comprehensive data analysis, the implementation of a uniform transplantation data collection form encompassing key elements relevant to the specific characteristics and heterogeneities of AdvSM and alloHCT is of utmost importance.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

JL and DC have assessed and verified the data. JL, DC, AR and JP contributed to concept and design. JL, DC, AR and JP were involved in acquisition of data. JL and DC contributed to statistical analysis. JL, DC, JS, EJ, AR and JP were involved in interpretation of data. All authors were involved in manuscript writing. All authors contributed to critical revision of the manuscript and for important intellectual content. All authors read and approved the final manuscript. All authors are accountable for all aspects of the work.

FUNDING

Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

DC received consulting fees from Blueprint Medicines, Novartis, Pfizer and BeiGene, honoraria from Blueprint Medicines, Novartis and AstraZeneca and travel support from Amgen and Janssen. JS received consulting fees from Blueprint Medicines and GlaxoSmithKline, honoraria from Blueprint Medicines, GlaxoSmithKline and Novartis and research funding from GlaxoSmithKline. KS received consulting fees from Blueprint Medicines, honoraria from Astra Zeneca and Novartis and participated in the speakers bureau of BMS. MJ received consulting fees from Novartis and honoraria from Amgen, Blueprint Medicines, BMS, Jazz Pharmaceuticals, Novartis and Pfizer. KS received consulting fees and honoraria from Blueprint Medicines, BMS and Novartis, lecture fees from GlaxoSmithKline and research support from Active Biotech. IK received consulting fees from Novartis, honoraria from AbbVie, Medac, Novartis and Takeda and travel support from Medac, Amgen, BeiGene, Jazz Pharmaceuticals, Janssen and Fondation Internationale Menarini. ES received consulting fees from Jazz Pharmaceuticals, BMS, Kite Gilead and Takeda, honoraria from Jazz Pharmaceuticals, BMS, Kite Gilead and Novartis and support for meeting attendance from Jazz Pharmaceuticals and Kite Gilead. SS received honoraria from Prothena, Janssen, Takeda and Pfizer, research funding from Prothena, Janssen and Sanofi and travel support from Prothena, Janssen, Celgene, Binding Site and Jazz Pharmaceuticals. MR received honoraria from BMS, Novartis, Takeda, Incyte, Corat, Cogent Biosciences, TEVA, Otsuka, Lilly, Abbvie, Pfizer, Beigene and GlaxoSmithKline, research funding from Novartis and travel support from BMS, Novartis, Abbvie, Jazz Pharmaceuticals, Daiichi Sankyo, Amgen, Astellas, SOBI and AOP. THB received consulting fees from Gilead, Janssen, Merck, Novartis and Pfizer, honoraria from Janssen, Merck and Novartis, research funding from Novartis and Pfizer, participated in the speakers bureaus of Gilead, Janssen, Merck, Novartis and Pfizer and was paid for patents and royalties from Novartis. SK received honoraria from Amgen. EJ received honoraria from BMS, Jazz Pharmaceuticals and Amgen and travel support from Medac. AR received consulting fees, honoraria and research funding from Abbvie, AOP Orphan Pharmaceuticals, Blueprint Medicines Corporation, BMS, GlaxoSmithKline, Incyte and Novartis and was member on an entity's Board of Directors or advisory committees of Abbvie, AOP Orphan Pharmaceuticals, Blueprint Medicines, BMS, GSK, Incyte and Novartis. JP received consulting fees from Amgen, Apellis Pharmaceuticals, BMS, MSD and Sanofi and was member on an entity's Board of Directors or advisory committees and Speakers Bureau of Alexion, AstraZeneca Rare Disease, Boehringer Ingelheim, Blueprint Medicines, Novartis, Pfizer, Samsung Bioepis, SOBI and F. Hoffmann-La Roche Ltd. The other authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41375-024-02186-x>.

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