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ORIGINAL REPORT

Hematopoietic Stem-Cell Transplantation for Advanced Systemic Mastocytosis

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ABSTRACT

Purpose
Advanced systemic mastocytosis (SM), a fatal hematopoietic malignancy characterized by drug resistance, has no standard therapy. The effectiveness of allogeneic hematopoietic stem-cell transplantation (alloHCT) in SM remains unknown.

Patients and Methods
In a global effort to define the value of HCT in SM, 57 patients with the following subtypes of SM were evaluated: SM associated with clonal hematologic non–mast cell disorders (SM-AHNMD; n = 38), mast cell leukemia (MCL; n = 12), and aggressive SM (ASM; n = 7). Median age of patients was 46 years (range, 11 to 67 years). Donors were HLA-identical (n = 34), unrelated (n = 17), umbilical cord blood (n = 2), HLA-haploidentical (n = 1), or unknown (n = 3). Thirty-six patients received myeloablative conditioning (MAC), and 21 patients received reduced-intensity conditioning (RIC).

Results
Responses in SM were observed in 40 patients (70%), with complete remission in 16 patients (28%). Twelve patients (21%) had stable disease, and five patients (9%) had primary refractory disease. Overall survival (OS) at 3 years was 57% for all patients, 74% for patients with SM-AHNMD, 43% for those with ASM, and 17% for those with MCL. The strongest risk factor for poor OS was MCL. Survival was also lower in patients receiving RIC compared with MAC and in patients having progression compared with patients having stable disease or response.

Conclusion
AlloHCT was associated with long-term survival in patients with advanced SM. Although alloHCT may be considered as a viable and potentially curative therapeutic option for advanced SM in the meantime, given that this is a retrospective analysis with no control group, the definitive role of alloHCT will need to be determined by a prospective trial.

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INTRODUCTION

Systemic mastocytosis (SM) is a hematopoietic stem-cell disease defined by clonal expansion of mast cells in various organs. SM comprises a pathologically and clinically heterogeneous group of disease variants with variable prognoses.[1-5] The clinically indolent forms do not shorten life expectancy and require cytoreductive therapy, whereas advanced SM variants, including mast cell leukemia (MCL), SM with associated clonal hematologic non–mast cell lineage disease (SM-AHNMD), and aggressive systemic mastocytosis (ASM), are associated with survival rates ranging from months to a few years despite cytoreductive therapy.[1,4,6,7]

No standard treatment exists for advanced SM. Cytoreductive therapy with cladribine or interferon alfa has been used, but no long-lasting responses have been reported.[8-10] A majority of patients with SM (> 80%) have a gain of function mutation in the gene encoding the tyrosine kinase KIT, usually KIT^{D816V}.[11-17] Although various tyrosine kinase

inhibitors have been tested in advanced SM,[18-26] their clinical benefit seems to be limited.[1,18,19,23] Allogeneic hematopoietic stem-cell transplantation (alloHCT) has curative potential for hematologic malignancies such as acute myelogenous leukemia (AML).[27] Although alloHCT has been used to treat life-threatening SM and hematologic malignancies associated with SM,[28-40] the outcome of alloHCT in patients with advanced SM has never been systematically studied. Indeed, the largest published case series consisted of only three patients.[37]

The purpose of this retrospective study was to evaluate the clinical outcomes of alloHCT in advanced SM and to assess potential benefits and hazards of alloHCT in all identifiable cases in the United States and Europe.

PATIENTS AND METHODS

Patients were included in the study if they underwent alloHCT for the treatment of SM-AHNMD, MCL, or ASM and if their data on mast cells—and AHNMD in case of SM-AHNMD—were available at both time points (before and after alloHCT). In case of SM-AHNMD, only patients whose SM component was known at the time of AHNMD diagnosis or before alloHCT were included, whereas patients whose SM component was discovered later (ie, hidden and/or occult mastocytosis) in a study were excluded. All these patients were indeed suffering from overt advanced mastocytosis requiring therapy. Note that in all of our patients, overt SM was documented and that any type of myelodysplastic syndrome (MDS) or AML that occurred in the context of SM was regarded as secondary and part of the entire clonal disease process (SM-AHNMD). Patients were identified at individual major transplantation or SM centers in the United States and Europe (the European Competence Network on Mastocytosis was the main source), the Center for International Blood and Marrow Transplant Research, and published reports. After approval by the individual center's institutional research board, information on patients was collected anonymously by using a data collection form. The diagnosis of SM was confirmed by a local investigator before reporting data to the data collection center at the University of Minnesota. Fifty-seven patients were identified: the data on 52 patients (43 never published and nine published) were obtained from 33 individual institutions (Appendix Tables A1, A2, and A3, online only).[28,29,33,37-40] The remaining five patients were identified from the literature, but no contact with the respective centers for participation was secured.[30,32,34-36] Data on surviving patients were updated during the study period of more than 2 years.

Response Evaluation in SM

Given the limitations of obtaining detailed source data for all patients, we could not use the SM response criteria developed by Valent et al[41] or the consensus statement developed by the International Working Group-Myeloproliferative Neoplasms Research and Treatment and the European Competence Network on Mastocytosis.[42] Therefore, three parameters were used to assess response in SM: the percentage of bone marrow mast cells, serum tryptase levels, and organ involvement. Organ involvement in SM at the time of diagnosis and changes over time (ie, improved, stable, or progressing) were reported and were included in the criteria used to determine responses (ie, laboratory measures, physical examination, imaging, or a combination thereof). Response was defined as $\geq$ 50% decrease in both serum tryptase levels and bone marrow mast cell percentage from biopsies (not aspirates) when both tests were available or, if the results of only one test were available, $\geq$ 50% improvement in one test if the results were corroborated by clinical determination of improvement and the absence of worsening of any other organ involvement. The lowest level of response was recorded if there was inconsistency among these three parameters. Complete response (CR) was defined as resolution of SM in all organs along with normalization of serum tryptase levels. Progression was defined as $\geq$ 50% increase in any of the three parameters, and stable disease was defined as less than 50% change in all three parameters. Although quantitative assessment was desirable for response evaluation, qualitative assessment that clearly indicated outcome (eg, worsened, increased, no evidence of mast cells in biopsies) was used in few patients. Because this is a retrospective analysis, there were no predetermined uniform time points for response evaluations. However, a vast majority of patients were evaluated at day 100, at relapse of hematologic malignancy or SM, or at progression of SM. Duration of response was analyzed in 36 patients (nonresponders are excluded as well as four responders with missing time of response). Response assessments were made independently by C.U., C.A., and P.V., and each investigator who provided patient information confirmed the final assigned response. In some patients, the local hematopathologist re-evaluated the original bone marrow specifically for mast cell burden. Response was accepted as reported to the French Registry by the individual institutions (n = 5; patients 42 to 46, and as previously published (n = 5; patients 1, 6, 12, 14, and 16). Treatment history in these patients was focused on SM-directed cytoreductive therapy that consisted primarily of interferon, steroids, tyrosine kinase inhibitors, and cladribine, but included other agents such as hydroxyurea, thalidomide, gemtuzumab ozogamicin, arsenic trioxide, cyclosporine, fludarabine, and cytarabine.

Statistical Analysis

Patient and disease characteristics were summarized by disease type. Cumulative incidence of treatment-related mortality was calculated with relapse as a competing risk. Kaplan-Meier estimations and the log-rank test were used to estimate and compare overall survival (OS) and progression-free survival (PFS) from time of transplantation. At the beginning of the study, the poor prognosis of patients with MCL was apparent and, therefore, we excluded these patients from univariable analysis of OS and PFS to eliminate possible confounding of MCL with other effects. We defined a P value of $\leq$ .05 as significant in the univariable analysis of risk factors for survival. Analysis was performed by using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient, Donor, and AlloHCT Characteristics

Fifty-seven patients with advanced SM underwent alloHCT between 1990 and May 2013 (Table 1). The majority of patients (n = 38, including one patient with MCL-AML and one patient with myelomastocytic leukemia) were diagnosed with SM-AHNMD, with the most common AHNMD being AML (n = 20, including one patient with myelomastocytic leukemia). Most patients had SM involvement in at least one extramedullary organ or tissue, primarily in the spleen (n = 33), liver (n = 26), skin (n = 12), and lymph nodes (n = 11). The most frequent recurrent cytogenetic abnormality was t(8;21)(q22,q22) (n = 5), and the most frequent molecular abnormality was KIT^{D816V} (n = 21). Of 20 patients with AML, 11 had abnormal cytogenetics, and nine had a *KIT* mutation, 17 received anthracycline plus cytarabine for induction, and six had persisting leukemia at the time of alloHCT. Patient and disease characteristics for each patient are detailed in Appendix Table A1.

Most patients received either sibling or unrelated alloHCT, although two patients received alloHCT from umbilical cord blood (UCB) and one received alloHCT from an HLA-haploidentical relative (Table 2). All patients received HLA-matched alloHCT except three patients whose unrelated donors were 9/10 HLA-locus and allele matched, two patients whose UCB was 5/6 HLA matched, and one patient whose HLA-haploidentical donor was 4/8 matched. Although the majority of patients (63%) received myeloablative conditioning (MAC), more than a third of patients received reduced-intensity conditioning (RIC). Detailed information on donor characteristics and alloHCT for individual patients is provided in Appendix Table A2.

Table 1. Patient and Donor Characteristics in Different SM Subtypes

Characteristic	ASM		MCL		SM-AHNMD		Total	
	No.	%	No.	%	No.	%	No.	%
No. of patients	7		12		38		57	
Age, years								
Median	50		43		45		46	
Range	31-62		13-60		11-67		11-67	
Male sex	4	57	5	42	21	55	30	53
KIT mutations								
Positive	1	14	4	33	19	50	24	42
Negative	0	0	4	33	5	13	9	16
Not reported	6	86	4	33	14	37	24	42
Cytogenetics								
Normal	3	43	6	50	16	42	25	44
t(8;21) or its variants	0	0	0	0	5	13	5	9
Abnormal (other than t(8;21))	0	0	4	33	10	26	14	25
Not reported	4	57	2	17	7	18	13	23
No. of involved organs (in addition to bone marrow)								
0	3	43	1	8	8	21	12	21
1-2	3	43	5	42	15	39	23	40
≥ 3	0	0	6	50	12	32	18	32
Not reported	1	14	0	0	3	8	4	7
No. of SM treatment categories								
0	0	0	2	17	21	55	23	40
1-2	3	43	7	58	9	23	19	33
≥ 3	2	29	3	25	7	18	12	21
Not reported	2	29	0	0	1	3	3	5
Time from SM diagnosis to alloHCT								
Median	19		9		9		9	
Range	7-192		3-216		2-96		2-216	
Karnofsky performance score								
≥ 90	0	0	5	42	16	42	21	37
< 90	3	43	4	33	9	24	16	28
Not reported	4	57	3	25	13	34	20	35
Donor								
Sibling	4	57	5	42	25	66	34	60
Unrelated	2	29	5	42	10	26	17	30
UCB or haploidentical	0	0	2	17	1	3	3	5
Not reported	1	13	0	0	2	5	3	5
Donor age, years								
Median	32		39		44		42	
Range	22-54		21-52		23-65		21-65	
Recipient-donor sex mismatched								
Matched	2	29	6	50	23	61	31	54
Mismatched	4	57	5	42	13	34	22	39
Not reported	1	14	1	8	2	5	4	7

Abbreviations: alloHCT, allogeneic hematopoietic stem-cell transplantation; ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHNMD, SM with an associated clonal hematologic non–mast cell lineage disease; UCB umbilical cord blood.

Disease Responses After AlloHCT

Responses were assigned to 12 patients with one criterion, 30 patients with two criteria, and 10 patients with all three criteria. Overall, SM responded to alloHCT in 40 patients (70%; Tables 2 and 3). The median bone marrow biopsy number after transplantation was 2.2. The median bone marrow mast cell percentage in biopsies (21% [range, 2% to 90%] before alloHCT *v* 1.8% [range, 0% to 90%] after alloHCT) and serum tryptase levels (130 ng/mL [range, 11 to 889 ng/mL] before alloHCT and 16 ng/mL [range, 2 to 404 ng/mL] after alloHCT) decreased significantly after alloHCT in patients with data available for before and after alloHCT (Figs 1A to 1D). In this comparison, the best values after alloHCT were used, and the median time to reach the best responses for both variables was 3 months (range, 1 to 36 months) after alloHCT. Of the 40 responding patients, 16 (28%) achieved CR (*KIT* mutations were negative in two of two patients with CR when tested after alloHCT). Twelve patients (21%) had stable disease. Patients with MCL had more primary resistance (three of five patients) and progression after initial response (three of 10 patients). The median time of response duration was 20 months. All 38 patients with SM-AHNMD achieved CR regarding the AHNMD component, but 10 subsequently relapsed with AHNMD, and

Table 2. AlloHCT Treatment, Complications, and Outcomes in Different SM Subtypes

Variable	ASM			MCL			SM-AHNMD			Total		
	No.	%	90% CI	No.	%	90% CI	No.	%	90% CI	No.	%	90% CI
No. of patients	7			12			38			57		
Conditioning												
Reduced intensity	4	57		3	25		14	37		21	37	
Myeloablative	3	43		9	75		24	63		36	63	
With TBI	1	14		3	25		12	32		16	28	
Transplantation year												
1990-2004	1	14		6	50		14	37		21	37	
2005-2013	6	86		6	50		24	63		36	63	
GVHD prophylaxis												
Methotrexate	3	43		6	50		19	50		28	49	
No methotrexate	2	29		5	42		16	42		23	40	
Not reported	2	29		1	8		3	8		6	11	
Tacrolimus	0	0		3	25		9	24		12	21	
Cyclosporine	5	71		4	33		24	63		33	58	
Not reported	2	29		5	42		5	13		12	21	
Response in SM												
Primary resistance	1	14		3	25		1	3		5	9	
Stable disease	1	14		0	0		11	30		12	21	
Response	5	72		9	75		26	68		40	70	
Complete remission	3	43		3	25		10	26		16	28	
Acute GVHD*												
None or grade 1	5	71		6	50		19	50		30	53	
Grade 2 to 4	2	29		5	42		16	42		23	40	
Not reported	0	0		1	8		3	8		4	7	
Chronic GVHD*												
None	3	43		8	67		12	32		23	40	
Limited or extensive	3	43		0	0		21	55		24	42	
Extensive	1	14		0	0		12	32		13	23	
Not reported	1	14		4	33		5	13		10	18	
Transplantation-related mortality												
6 months		14	1 to 30		25	6 to 44		5	1 to 11		11	4 to 17
1 year		14	1 to 30		33	12 to 54		17	7 to 27		20	11 to 28
Overall survival												
1 year		43	14 to 70		25	8 to 46		78	64 to 87		62	50 to 72
3 years		43	14 to 70		17	4 to 37		74	60 to 84		57	46 to 68
Progression-free survival												
1 year		43	14 to 70		17	4 to 37		70	55 to 80		55	44 to 65
3 year		43	14 to 70		17	4 to 37		63	47 to 75		51	39 to 61

Abbreviations: alloHCT, allogeneic hematopoietic stem-cell transplantation; ASM, aggressive systemic mastocytosis; GVHD, graft-versus-host disease; MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHNMD, SM with an associated clonal hematologic non–mast cell lineage disease; TBI, total body irradiation.
*Total incidence.

five of these died. Details of treatment and outcome are given in Appendix Table A3.

OS and PFS for all patients were 62% (90% CI, 50% to 72%) and 57% (90% CI, 44% to 65%) at 1 year, and 55% (90% CI, 46% to 68%) and 51% (90% CI, 39% to 61%) at 3 years, respectively (Figs 2A and 2B; Tables 2 and 3). OS and PFS were significantly higher in patients with SM-AHNMD and were lowest in patients with MCL (Figs 2C and 2D; $P < .01$). No deaths or relapses were observed after 15 and 24 months, respectively. The median follow-up among survivors was 32 months (range, 3 to 202 months).

Factors Affecting PFS and OS

Univariable analysis of relevant variables and outcomes are shown in Table 3. The strongest risk factor for worse OS was a diagnosis of MCL. Other risk factors were evaluated after excluding patients with MCL (n = 12). In the 45 remaining patients, factors that had an effect on survival included a diagnosis of ASM and RIC (Figs 2E and 2F). The median age for patients receiving MAC regimens was 38 years (range, 11 to 62 years) compared with 50 years (range, 17 to 67 years) for patients receiving RIC. The superior outcome with MAC was not fully accounted for by younger patient age; for patients older than age 40 years, 1-year OS was 85% after MAC (n = 13) and 51% after RIC (n = 16). RIC was used as frequently in the entire study cohort as in patients with Karnofsky performance status (KPSs) $\leq$ 80%, (21 [37%] of 57 and four [25%] of 16, respectively). A lower KPS before alloHCT seemed to lower survival, and six of seven patients with KPSs $\leq$ 70% died. OS at 1 year was shorter for patients with progression (20%; 90% CI, 2% to 52%) compared with patients with stable disease (89%; 90% CI, 54% to 98%) and with responders (63%; 90% CI, 49% to 74%; Fig 2G).

Table 3. Factors Associated With OS and SM PFS in Patients With no MCL Only (n = 45)

Factor	No.	%	OS			PFS		
			1-Year	90% CI	*P**	1-Year	90% CI	*P**
Diagnosis								
ASM	7	16	43	14 to 70	.05	43	14 to 70	.07
SM-AHNMD	38	84	78	64 to 87		70	55 to 80	
AML, ALL, MML	21	47	75	55 to 87	.75	65	45 to 80	.53
MDS, MPN, MM	17	38	81	57 to 92		75	52 to 88	
Age, years								
< 40	16	36	80	56 to 92	.39	68	44 to 83	.85
≥ 40	29	64	67	50 to 80		65	48 to 77	
Sex								
Female	20	44	79	58 to 90	.34	74	54 to 87	.32
Male	25	56	65	46 to 79		59	40 to 73	
KIT mutations								
Negative	5	11	60	19 to 85	.27	40	9 to 71	.40
Positive	20	44	82	60 to 93		74	53 to 87	
Unknown	20	44	65	40 to 81		65	40 to 82	
Cytogenetics								
Normal	19	42	68	47 to 82	.61	68	47 to 82	.92
t(8;21)	5	11	100			60	19 to 85	
Other	10	22	67	35 to 86		67	35 to 86	
Unknown	11	24	69	38 to 87		62	34 to 82	
Treatment for SM								
None	21	47	79	59 to 90	.11	70	49 to 83	.27
One to two agents	12	27	81	51 to 94		74	46 to 89	
Three or more agents	9	20	44	18 to 68		44	18 to 68	
Karnofsky performance score								
< 90	12	27	48	23 to 69	.15	49	24 to 70	.28
≥ 90	16	36	80	56 to 92		80	56 to 92	
Unknown	17	38	82	60 to 93		64	42 to 80	
AML CR status								
In CR	14	31	79	54 to 91	.63	71	46 to 86	.37
Not in CR	6	13	60	19 to 85		42	9 to 72	
Percentage of BM mast cells before transplantation								
< 20	14	31	68	42 to 85	.87	53	29 to 73	.33
≥ 20	15	33	73	49 to 87		73	49 to 87	
Time from diagnosis to alloHCT, months								
≤ 13	29	64	78	62 to 88	.23	71	54 to 83	.27
> 13	16	36	60	36 to 77		56	34 to 74	
Conditioning								
Reduced intensity	18	40	57	34 to 74	.10	48	27 to 66	.03
Myeloablative	27	60	81	65 to 91		77	61 to 88	
Myeloablative with TBI	13	29	85	59 to 95	.98	85	59 to 95	.59
Myeloablative without TBI	13	29	84	57 to 95		76	49 to 90	
Graft source								
BM	16	36	75	52 to 88	.86	75	52 to 88	.32
PBSCs	27	60	72	54 to 84		62	45 to 75	
Donor age, years								
< 40	11	24	64	35 to 82	.31	64	35 to 82	.43
≥ 40	23	51	76	55 to 87		76	57 to 88	
Donor sex match								
Match	25	56	80	62 to 90	.21	72	54 to 84	.18
Female donor, male recipient	10	22	44	18 to 68		34	11 to 59	
Male donor, female recipient	7	16	71	34 to 90		71	34 to 90	
Donor relation								
Sibling	29	64	74	56 to 85	.50	64	47 to 77	.95
Unrelated	12	27	67	40 to 84		67	40 to 84	
Other (UCB)	1	2	0			0		

(continued on following page)

Table 3. Factors Associated With OS and SM PFS in Patients With no MCL Only (n = 45) (continued)

Factor	No.	%	OS			PFS		
			1-Year	90% CI	*P**	1-Year	90% CI	*P**
aGVHD								
None or grade 1	24	53	73	49 to 87	.49	69	46 to 84	.55
Grade 2 to 4	18	40	66	44 to 81		61	35 to 79	

Abbreviations: aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic stem-cell transplantation; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; BM, bone marrow; CR, complete response; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MML, myelomastocytic leukemia; MPN, myeloproliferative neoplasia; OS, overall survival; PBSC, peripheral blood stem cell; PFS, progression-free survival; SM, systemic mastocytosis; SM-AHNMD, SM with an associated clonal hematologic non–mast cell lineage disease; TBI, total body irradiation; UCB, umbilical cord blood.
**P* value is from univariable analysis.

Factors without any identifiable impact on OS and PFS were patient age, donor age, donor type (sibling or unrelated donor), graft source (bone marrow or peripheral blood stem cells), bone marrow mast cell percentage at alloHCT, *KIT* mutation status, cytogenetic groupings, total body irradiation used in MAC regimens, and CR status at alloHCT (Table 3). OS and PFS at 1 year were not affected by whether or not the patient received prior SM-directed cytoreductive therapy (Table 3). When they were specifically evaluated in patients with SM-AHNMD only, OS and PFS were again similar (73% and 68% for patients with history of prior SM-directed therapy [41%] compared with 79% and 70% for those who did not receive therapy [55%], respectively).

All patients who received alternative donor transplants (two UCB and one HLA-haploidentical relative) and all patients with MCL who received RIC (n = 3) died. In contrast, all five patients with t(8;21) or its variant survived.

Donor Lymphocyte Infusions and Second AlloHCT

Six of 10 patients who received donor lymphocyte infusions (DLIs) for mixed chimerism and/or stable SM disease responded to this treatment (three achieved CR, of which two were durable). However, three patients who received DLIs for SM progression (n = 2) or graft failure with AML relapse (n = 1) had no response and died (Appendix Table A3).

A second alloHCT (two RIC and one MAC regimen) was performed for relapse of myelomastocytic leukemia (n = 1), relapse of AML (n = 1), and progression of both MDS and SM (n = 1) at 4, 5, and 44 months after the first alloHCT, respectively. All three patients were alive in CR of SM or hematologic malignancy after the second alloHCT (Appendix Table A3).

AlloHCT Complications

Treatment-related mortality at 6 months and 1 year was 11% and 20%, respectively, and was highest in MCL (25% and 33%; Table 2). Primary and secondary engraftment failure each occurred in one patient. In the first 100 days after initiation of alloHCT conditioning, symptoms possibly related to mast cell degranulation occurred in five patients and included hot flashes (n = 3), skin rash (n = 1), and abdominal cramps and nausea (n = 1). Acute graft-versus-host disease (GVHD) grades 2 to 4 and chronic extensive GVHD occurred in 40% and 23% of patients, respectively (Table 2). Two patients died from complications related to severe acute GVHD (Appendix Table A3).

DISCUSSION

This study has found that alloHCT can confer long-term OS in patients with advanced SM. The greatest survival benefit was observed in patients with SM-AHNMD who had a 3-year survival probability of 74%. The reported median OS of patients with SM-AHNMD without alloHCT was 2 years.[6] Favorable OS in our group is especially significant, given that approximately one third of the patients with AML had active disease at transplantation—an indisputably poor prognostic factor for outcomes after alloHCT.[27,43-49] Although the t(8;21)(q22,q22) translocation is considered a favorable prognostic factor in patients with AML without SM,[50-52] patients with AML with the same cytogenetic abnormality have poor prognosis in the presence of SM, even hidden and/or occult SM.[31,53,54] The presence of *KIT* mutations in patients with AML with t(8;21) is associated with poor prognosis regardless of the presence of SM.[55-60] Most of our patients with SM-AML had *KIT* mutations. It is possible that not all patients had aggressive SM at the diagnosis of AHNMD, given that C findings (clinical findings related to organs involved in SM, eg, pancytopenia) can be caused by the AHNMD component as well. However, regarding survival, there was no difference between patients who received SM-specific cytoreductive therapy before alloHCT (indicating aggressive SM) and those who did not. One can argue that AML diagnosed in the context of SM (or in the context of KIT^{D816V} in which an occult SM is often present) should always be judged as secondary AML and thus as high-risk (poor prognosis) disease regardless of the aggressiveness of SM. Together, our data suggest that alloHCT may overcome the unfavorable prognosis in patients with SM-AML. AlloHCT also provided long-term survival in approximately 40% of patients with ASM, which seems superior to reported survival rates in patients who did not have transplantations (median survival, 3.5 years without any evidence of a plateau).[6] Patients with MCL had the poorest outcome among all of the SM subtypes in the study. However, given that the reported median survival of patients with MCL without alloHCT is short (< 12 months), our results suggest that alloHCT may be beneficial for patients with MCL as well.[6,61] Evidence of treatment failure among the majority of patients with MCL was shown by early treatment–related mortality and rapid disease progression after initial responses. However, those responses, albeit transient, suggest that immunotherapy has an impact on MCL. The fact that the only long-term survivors were among patients prepared for alloHCT with high-intensity MAC regimens may indicate that the actual tumor burden

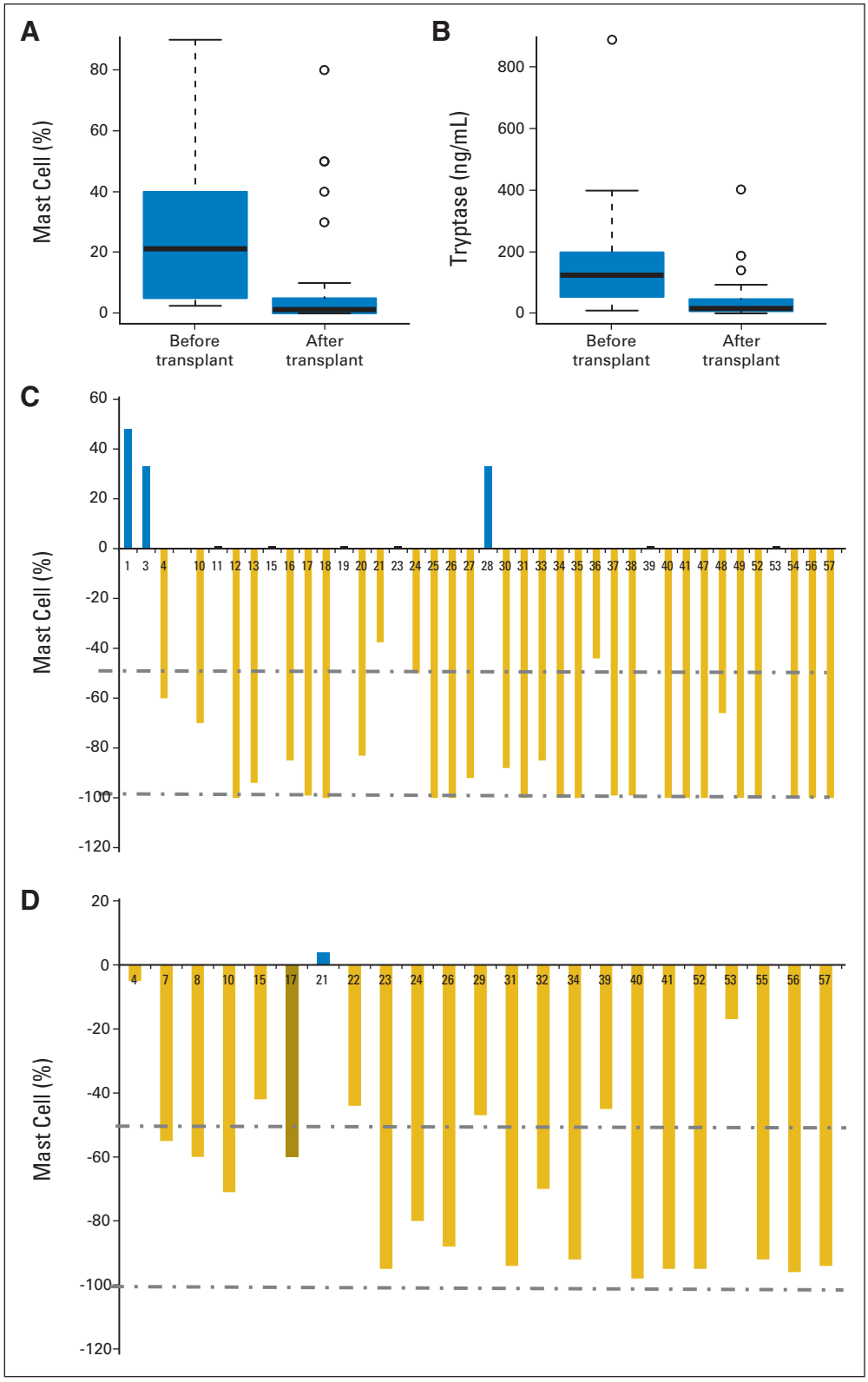

Fig 1. Allogeneic hematopoietic stem-cell transplantation (alloHCT) improves responses in patients with advanced systemic mastocytosis. Changes in (A) bone marrow cell percentage (n = 39; $P < .01$) and (B) serum tryptase levels (n = 23; $P < .01$) in patients with before and after alloHCT data available. The post-transplantation data represent the best (lowest) values of both mast cell percentage and serum tryptase, both of which were observed a median of 3 months (range, 1 to 36 months) after alloHCT. The median and interquartile range are indicated by a solid line and rectangle, respectively. Observations outside the interquartile range are indicated by dashed lines or dots. Percentage change in mast cells in (C) bone marrow and (D) in serum tryptase levels in each patient with available before and after alloHCT data.

that has to be overcome by donor cells is a critical determinant influencing transplantation outcome. However, when compared with results in patients with SM-AHNMD (many of whom had AML that was not in remission at the time of alloHCT) or those with ASM, this pattern suggests that not only disease burden but also the intrinsic resistance of MCL cells was an important factor. In general, patients conditioned with myeloablative regimens fared better than patients prepared with reduced-intensity regimens; the advantage of lower

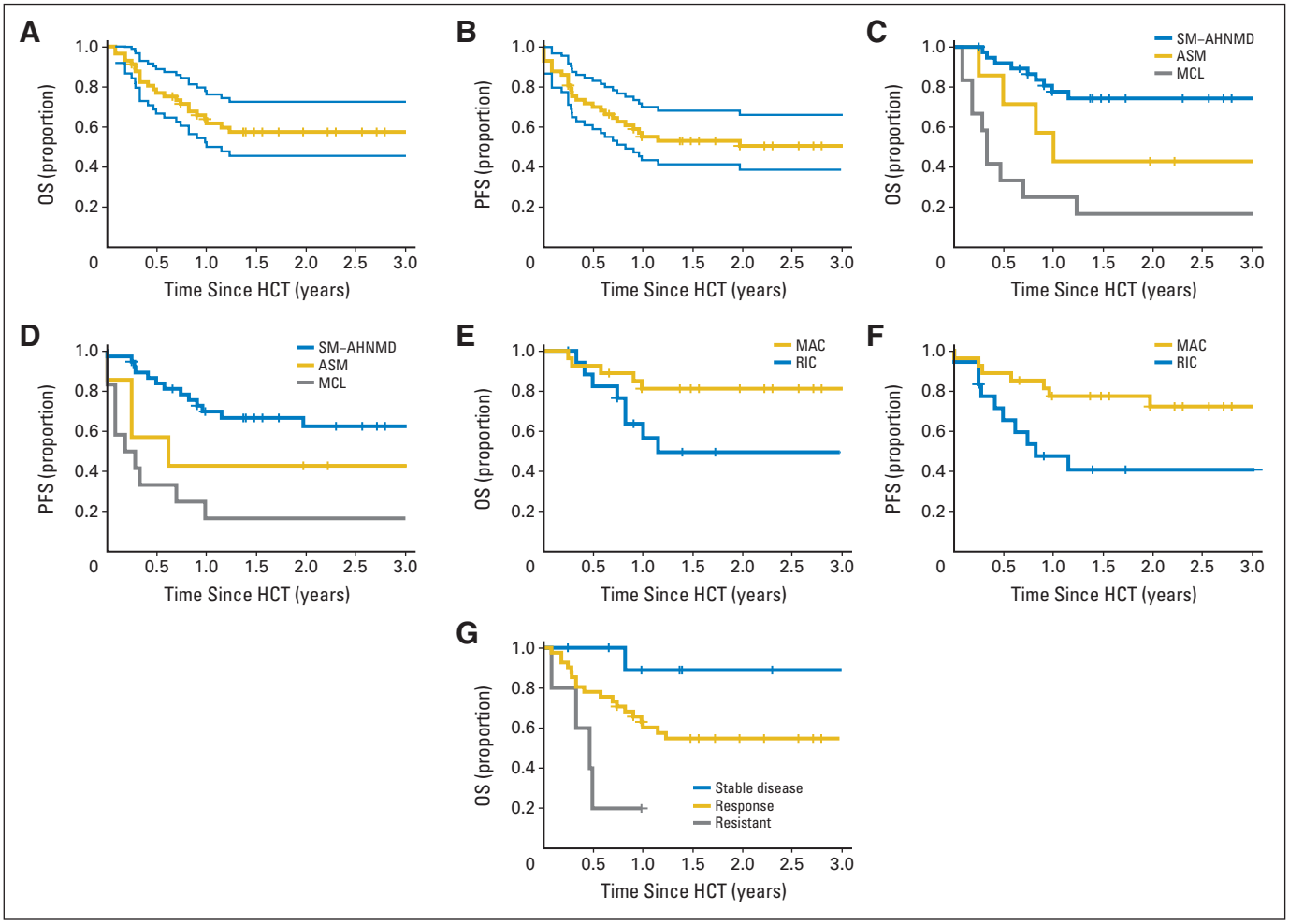

Fig 2. Allogeneic hematopoietic stem-cell transplantation (alloHCT or HCT) outcomes in patients with advanced systemic mastocytosis (SM). (A) Overall survival (OS) and (B) progression-free survival (PFS) for all patients with advanced SM. Blue lines represent 95% CIs. (C) OS and (D) SM PFS by type of systemic mastocytosis. (E) OS and (F) SM PFS by conditioning regimen intensity. (G) OS by initial response in SM. ASM, aggressive systemic mastocytosis; MAC, myeloablative conditioning; MCL, mast cell leukemia; RIC, reduced-intensity conditioning; SM-AHNMD, SM with an associated clonal hematologic non–mast cell lineage disease.

regimen-related mortality was canceled out by a higher progression incidence.[62,63] The observation that patients with a lower KPS ($\leq$ 70%) experienced higher mortality is consistent with results in many reports on various diseases showing the impact of performance status and comorbidities in particular on the outcome of alloHCT.[64,65]

Responses in SM were observed in 70% of the patients examined. However, because this is a retrospective analysis and thus there were no predetermined evaluation time points after alloHCT, the duration of response and PFS should be viewed with caution. Given that there is a decrease in serum tryptase levels after alloHCT that may reflect responses in the AHNMD component (eg, AML or MDS)[66-68] itself, response evaluation mainly depended on bone marrow mast cell percentage. Responses (observed after RIC and MAC regimens and DLI) were often durable and sometimes developed gradually over years, suggesting that donor-derived cells induced a potent graft-versus-mastocytosis effect. Mast cells have been shown to express HLA class I and, at least under certain conditions such as in vitro stimulation of mast cells by interferon gamma, class II antigens.[69-72] These antigens are critical for eliciting a graft-versus-tumor effect through alloreactive T cells and natural-killer cells.[73] The apparent plateau of both OS and PFS suggests that alloHCT can be curative in some patients with SM. AlloHCT conferred long-term survival not only for the responders but also for the patients having stable disease. Most of the patients with stable disease had AHNMD as well; therefore, benefiting from alloHCT necessitates curing AHNMD but not the SM component. Another explanation could be that perhaps a longer time is needed to observe improvements in the SM component compared with AHNMD in some patients with SM-AHNMD.

SM-specific complications, including anaphylactoid or severe mediator-related reactions[74] due to rapid lysis of mast cells and graft failure due to marrow fibrosis, were rare. Low incidence of graft failure might result from the role of mast cells in increasing allograft tolerance. Healthy mast cells are crucial for skin allograft tolerance, probably through regulatory T-cell–dependent peripheral tolerance in mice.[75] The frequency of acute and chronic GVHD was similar to that seen in the overall alloHCT population.[76,77]

Although this study has several limitations because of its retrospective nature, it summarizes transplantation results from the largest cohort of patients with this rare and fatal disease: alloHCT is reasonably safe, and overall outcome is promising. These data

support a prospective study in which before-and-after-alloHCT means should be used to further improve outcomes in patients with ASM and MCL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Valent P, Horny HP, Escribano L, et al: Diagnostic criteria and classification of mastocytosis: A consensus proposal. Leuk Res 25:603-625, 2001
2. Robyn J, Metcalfe DD: Systemic mastocytosis. Adv Immunol 89:169-243, 2006
3. Escribano L, Alvarez-Twose I, Sánchez-Muñoz L, et al: Prognosis in adult indolent systemic mastocytosis: A long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol 124:514-521, 2009
4. Horny HP, Metcalfe DD, Bennet JM, et al: Mastocytosis, in Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4). Lyon, France, IARC, 2008, pp 54-63
5. Ustun C, Savage NM, Gotlib J, et al: Systemic mastocytosis with associated clonal hematological non-mast-cell lineage disease: A case review. Am J Hematol 87:191-193, 2012
6. Lim KH, Tefferi A, Lasho TL, et al: Systemic mastocytosis in 342 consecutive adults: Survival studies and prognostic factors. Blood 113:5727-5736, 2009
7. Pardanani A, Lim KH, Lasho TL, et al: Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. Blood 114:3769-3772, 2009
8. Valent P, Sperr WR, Akin C: How I treat patients with advanced systemic mastocytosis. Blood 116:5812-5817, 2010
9. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al: Cladribine therapy for systemic mastocytosis. Blood 102:4270-4276, 2003
10. Kluin-Nelemans HC, Jansen JH, Breukelman H, et al: Response to interferon alfa-2b in a patient with systemic mastocytosis. N Engl J Med 326:619-623, 1992
11. Kitamura Y, Hirotab S: Kit as a human oncogenic tyrosine kinase. Cell Mol Life Sci 61:2924-2931, 2004
12. Akin C: Clonality and molecular pathogenesis of mastocytosis. Acta Haematol 114:61-69, 2005
13. Nakata Y, Kimura A, Katoh O, et al: c-kit point mutation of extracellular domain in patients with myeloproliferative disorders. Br J Haematol 91:661-663, 1995
14. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al: KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: A prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. Blood 108:2366-2372, 2006
15. Nagata H, Worobec AS, Oh CK, et al: Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci U S A 92:10560-10564, 1995
16. Longley BJ, Tyrrell L, Lu SZ, et al: Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: Establishment of clonality in a human mast cell neoplasm. Nat Genet 12:312-314, 1996
17. Longley BJ Jr, Metcalfe DD, Tharp M, et al: Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc Natl Acad Sci U S A 96:1609-1614, 1999
18. Ustun C, DeRemer DL, Akin C: Tyrosine kinase inhibitors in the treatment of systemic mastocytosis. Leuk Res 35:1143-1152, 2011
19. Akin C, Fumo G, Yavuz AS, et al: A novel form of mastocytosis associated with a transmembrane c-kit mutation and response to imatinib. Blood 103:3222-3225, 2004
20. Pardanani A, Elliott M, Reeder T, et al: Imatinib for systemic mast-cell disease. Lancet 362:535-536, 2003
21. Aichberger KJ, Sperr WR, Gleixner KV, et al: Treatment responses to cladribine and dasatinib in rapidly progressing aggressive mastocytosis. Eur J Clin Invest 38:869-873, 2008
22. Ustun C, Corless CL, Savage N, et al: Chemotherapy and dasatinib induce long-term hematologic and molecular remission in systemic mastocytosis with acute myeloid leukemia with KIT D816V. Leuk Res 33:735-741, 2009
23. Verstovsek S, Tefferi A, Cortes J, et al: Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clin Cancer Res 14:3906-3915, 2008
24. Gotlib J, Berubé C, Growney JD, et al: Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V KIT mutation. Blood 106:2865-2870, 2005
25. Gleixner KV, Mayerhofer M, Sonneck K, et al: Synergistic growth-inhibitory effects of two tyrosine kinase inhibitors, dasatinib and PKC412, on neoplastic mast cells expressing the D816V-mutated oncogenic variant of KIT. Haematologica 92:1451-1459, 2007
26. Gleixner KV, Mayerhofer M, Aichberger KJ, et al: PKC412 inhibits in vitro growth of neoplastic human mast cells expressing the D816V-mutated variant of KIT: Comparison with AMN107, imatinib, and cladribine (2CdA) and evaluation of cooperative drug effects. Blood 107:752-759, 2006
27. Gupta V, Tallman MS, Weisdorf DJ: Allogeneic hematopoietic cell transplantation for adults with acute myeloid leukemia: Myths, controversies, and unknowns. Blood 117:2307-2318, 2011
28. Sperr WR, Drach J, Hauswirth AW, et al: Myelomastocytic leukemia: Evidence for the origin of mast cells from the leukemic clone and eradication by allogeneic stem cell transplantation. Clin Cancer Res 11:6787-6792, 2005
29. Födinger M, Fritsch G, Winkler K, et al: Origin of human mast cells: Development from transplanted hematopoietic stem cells after allogeneic bone marrow transplantation. Blood 84:2954-2959, 1994
30. Przepiorka D, Giralt S, Khouri I, et al: Allogeneic marrow transplantation for myeloproliferative disorders other than chronic myelogenous leukemia: Review of forty cases. Am J Hematol 57:24-28, 1998
31. Pullarkat VA, Bueso-Ramos C, Lai R, et al: Systemic mastocytosis with associated clonal hematological non-mast-cell lineage disease: Analysis of clinicopathologic features and activating c-kit mutations. Am J Hematol 73:12-17, 2003
32. Rønnov-Jessen D, Løvgreen Nielsen P, Horn T: Persistence of systemic mastocytosis after

allogeneic bone marrow transplantation in spite of complete remission of the associated myelodysplastic syndrome. Bone Marrow Transplant 8:413-415, 1991

33. Pullarkat V, Bedell V, Kim Y, et al: Neoplastic mast cells in systemic mastocytosis associated with t(8;21) acute myeloid leukemia are derived from the leukemic clone. Leuk Res 31:261-265, 2007

34. Spyridonidis A, Thomas AK, Bertz H, et al: Evidence for a graft-versus-mast-cell effect after allogeneic bone marrow transplantation. Bone Marrow Transplant 34:515-519, 2004

35. Nagai S, Ichikawa M, Takahashi T, et al: The origin of neoplastic mast cells in systemic mastocytosis with AML1/ETO-positive acute myeloid leukemia. Exp Hematol 35:1747-1752, 2007

36. Chen TY, Chen JS, Huang WT, et al: Rapid engraftment of mast cells of donor origin in a case of acute myeloid leukemia with mast cell leukemia after allogeneic stem cell transplantation. Bone Marrow Transplant 32:111-114, 2003

37. Nakamura R, Chakrabarti S, Akin C, et al: A pilot study of nonmyeloablative allogeneic hematopoietic stem cell transplant for advanced systemic mastocytosis. Bone Marrow Transplant 37:353-358, 2006

38. Gromke T, Elmaagacli AH, Ditschkowski M, et al: Delayed graft-versus-mast-cell effect on systemic mastocytosis with associated clonal haematological non-mast cell lineage disease after allogeneic transplantation. Bone Marrow Transplant 48:732-733, 2013

39. Valentini CG, Rondoni M, Pogliani EM, et al: Mast cell leukemia: A report of ten cases. Ann Hematol 87:505-508, 2008

40. Chantorn R, Shwayder T: Death from mast cell leukemia: A young patient with longstanding cutaneous mastocytosis evolving into fatal mast cell leukemia. Pediatr Dermatol 29:605-609, 2012

41. Valent P, Akin C, Sperr WR, et al: Aggressive systemic mastocytosis and related mast cell disorders: Current treatment options and proposed response criteria. Leuk Res 27:635-641, 2003

42. Gotlib J, Pardanani A, Akin C, et al: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood 121:2393-2401, 2013

43. Oran B, Popat U, Rondon G, et al: Significance of persistent cytogenetic abnormalities on myeloablative allogeneic stem cell transplantation in first complete remission. Biol Blood Marrow Transplant 19:214-220, 2013

44. Warlick ED, Cioc A, Defor T, et al: Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: Importance of pretransplant disease burden. Biol Blood Marrow Transplant 15:30-38, 2009

45. Gyurkocza B, Storb R, Storer BE, et al: Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. J Clin Oncol 28:2859-2867, 2010

46. Sayer HG, Kröger M, Beyer J, et al: Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia: Disease status by marrow blasts is the strongest prognostic factor. Bone Marrow Transplant 31:1089-1095, 2003

47. Duval M, Klein JP, He W, et al: Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. J Clin Oncol 28:3730-3738, 2010

48. Buckley SA, Appelbaum FR, Walter RB: Prognostic and therapeutic implications of minimal residual disease at the time of transplantation in acute leukemia. Bone Marrow Transplant 48:630-641, 2013

49. Ustun C, Wiseman AC, Defor TE, et al: Achieving stringent CR is essential before reduced-intensity conditioning allogeneic hematopoietic cell transplantation in AML. Bone Marrow Transplant 48:1415-1420, 2013

50. Estey EH: Acute myeloid leukemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 87:89-99, 2012

51. Byrd JC, Mrózek K, Dodge RK, et al: Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: Results from Cancer and Leukemia Group B (CALGB 8461). Blood 100:4325-4336, 2002

52. Slovak ML, Kopecky KJ, Cassileth PA, et al: Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: A Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood 96:4075-4083, 2000

53. Wang SA, Hutchinson L, Tang G, et al: Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease: Clinical significance and comparison of chromosomal abnormalities in SM and AHNMD components. Am J Hematol 88:219-224, 2013

54. Johnson RC, Savage NM, Chiang T, et al: Hidden mastocytosis in acute myeloid leukemia with t(8;21)(q22;q22). Am J Clin Pathol 140:525-535, 2013

55. Paschka P, Marcucci G, Ruppert AS, et al: Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): A Cancer and Leukemia Group B Study. J Clin Oncol 24:3904-3911, 2006

56. Boissel N, Leroy H, Brethon B, et al: Incidence and prognostic impact of c-Kit, FLT3, and Ras gene mutations in core binding factor acute myeloid leukemia (CBF-AML). Leukemia 20:965-970, 2006

57. Park SH, Chi HS, Min SK, et al: Prognostic impact of c-KIT mutations in core binding factor acute myeloid leukemia. Leuk Res 35:1376-1383, 2011

58. Cairoli R, Beghini A, Grillo G, et al: Prognostic impact of c-KIT mutations in core binding factor leukemias: An Italian retrospective study. Blood 107:3463-3468, 2006

59. Wang YY, Zhou GB, Yin T, et al: AML1-ETO and C-KIT mutation/overexpression in t(8;21) leukemia: Implication in stepwise leukemogenesis and response to Gleevec. Proc Natl Acad Sci U S A 102:1104-1109, 2005

60. Fritsche-Polanz R, Fritz M, Huber A, et al: High frequency of concomitant mastocytosis in patients with acute myeloid leukemia exhibiting the transforming KIT mutation D816V. Mol Oncol 4:335-346, 2010

61. Georgin-Lavialle S, Lhermitte L, Dubreuil P, et al: Mast cell leukemia. Blood 121:1285-1295, 2013

62. Shimoni A, Hardan I, Shem-Tov N, et al: Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: The role of dose intensity. Leukemia 20:322-328, 2006

63. Ringdén O, Labopin M, Ehninger G, et al: Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. J Clin Oncol 27:4570-4577, 2009

64. Marks DI, Wang T, Pérez WS, et al: The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. Blood 116:366-374, 2010

65. McClune BL, Weisdorf DJ, Pedersen TL, et al: Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol 28:1878-1887, 2010

66. Sperr WR, Mitterbauer M, Mitterbauer G, et al: Quantitation of minimal residual disease in acute myeloid leukemia by tryptase monitoring identifies a group of patients with a high risk of relapse. Clin Cancer Res 11:6536-6543, 2005

67. Sperr WR, El-Samahi A, Kundi M, et al: Elevated tryptase levels selectively cluster in myeloid neoplasms: A novel diagnostic approach and screen marker in clinical haematology. Eur J Clin Invest 39:914-923, 2009

68. Sperr WR, Jordan JH, Baghestanian M, et al: Expression of mast cell tryptase by myeloblasts in a group of patients with acute myeloid leukemia. Blood 98:2200-2209, 2001

69. Dimitriadou V, Mécheri S, Koutsilieris M, et al: Expression of functional major histocompatibility complex class II molecules on HMC-1 human mast cells. J Leukoc Biol 64:791-799, 1998

70. Banovac K, Ghandur-Mnaymneh L, Leone J, et al: Intrathyroidal mast cells express major histocompatibility complex class-II antigens. Int Arch Allergy Appl Immunol 90:43-46, 1989

71. Malaviya R, Twesten NJ, Ross EA, et al: Mast cells process bacterial Ags through a phagocytic route for class I MHC presentation to T cells. J Immunol 156:1490-1496, 1996

72. Kambayashi T, Allenspach EJ, Chang JT, et al: Inducible MHC class II expression by mast cells supports effector and regulatory T cell activation. J Immunol 182:4686-4695, 2009

73. Warren EH, Deeg HJ: Dissecting graft-versus-leukemia from graft-versus-host-disease using novel strategies. Tissue Antigens 81:183-193, 2013

74. Metcalfe DD, Peavy RD, Gilfillan AM: Mechanisms of mast cell signaling in anaphylaxis. J Allergy Clin Immunol 124:639-646, 2009

75. Lu LF, Lind EF, Gondek DC, et al: Mast cells are essential intermediaries in regulatory T-cell tolerance. Nature 442:997-1002, 2006

76. Weisdorf D: GVHD the nuts and bolts. Hematology Am Soc Hematol Educ Program 62-67, 2007

77. Devine SM, Adkins DR, Khoury H, et al: Recent advances in allogeneic hematopoietic stem-cell transplantation. J Lab Clin Med 141:7-32, 2003

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Appendix

Table A1. Patient and SM Characteristics

Author*	Country	Patient No.	Sex	Patient Age at AlloHCT (years)	Diagnosis	Year of Diagnosis of Primary SM	Cytogenetic Abnormality	*KIT* Mutation
Chen et al[36]	Taiwan	1	M	18	MCL-AML	2001	t(8;21)(q22;q22)	No
Devine	United States	2	M	36	SM-AHNMD (MPN-MDS with Eos)	1997	Normal	NA
Födinger et al[29]	Austria	3	F	11	SM-AHNMD (AML) progressed from MDS-RAEB-II)	1991	t(8;1)(q22,q21), de1(5)(q13,q23)	NA
Hsu	United States	4	M	62	ASM	2005	Normal	NA
Doubek	Czech Republic	5	M	57	ASM	2010	Normal	D816V
Nagai et al[35]	Japan	6	F	32	SM-AHNMD (AML)	2006	46XX, t(8;21) (q22;q22), del9 (q22;q34)	D816Y
Nakamura et al[37]	United States	7	M	49	SM-AHNMD (MPN with Eos)	1999	NA	D816V
Nakamura et al[37]	United States	8	F	50	SM-AHNMD (MDS-RA)	1998	NA	D816V
Nakamura et al[37]	United States	9	M	47	MCL (progressed from SM)	1996	NA	D816G
Valent	Austria	10	F	36	MCL	2005	Normal	No D816V found
Valent	Austria	11	F	44	SM-AHNMD (AML)	1995	NA	NA
Przepiorka et al[30]	United States	12	M	32	ASM	Approximately 1990	Normal	NA
Pullarkat et al[33]	United States	13	F	51	SM-AHNMD (AML)	2003	t(8;21) (q22;22) and del(9)(q12;q22)	D816V
Rønnov-Jessen et al[32]	Denmark	14	F	38	SM-AHNMD (AML)	1991	NA	NA
Sperr et al[28]	Austria	15	M	17	MML	2001	Complex: t(8;10;21)(q22;q21;q22), t(11;19)(q13;13), del(9)(q22)	No D816V found
Spyridonidis et al[34]	Germany	16	M	31	MCL	Approximately 2000	t(13;14) (q10;q10)	No codon 816 and 560 mutation found
Stuart	United States	17	M	56	SM-AHNMD (AML progressed from MDS)	2009	Normal	D816V
Popat	United States	18	M	46	MCL	2001	Diploidy	NA
Hogan	United States	19	M	61	SM-AHNMD (AML)	2011	Monosomy 7	D816V
Hogan	United States	20	F	26	SM-AHNMD (AML)	2010	Normal	D816V
Kreil	Germany	21	F	50	ASM	1991	NA	NA
Reiter	Germany	22	F	27	SM-AHNMD (AML)	2005	Normal	D816V
Gruhn	Germany	23	M	17	SM-AHNMD (MDS-RCMD)	2007	Normal	D816V
Reiter	Germany	24	M	65	SM-AHNMD (AML)	2008	Trisomy 8	D816V
Hermine	France	25	M	61	SM-AHNMD (AML)	2007	Trisomy 8	D816V
Gromke et al[38]	Germany	26	M	53	SM-AHNMD (AML)	2002	Normal	D816V
Tholouli	England	27	F	47	MCL, progressed from SM	2011	Complex: 43,XX,-1,add(2)(p?13),-4,add(5)(p15),-9,del(10)(q2?4q2?6),-11,-17,der(17)? t(11;17) (q13;q25), 20, +2mar,+r[4]/88,idemx2[1]/46,XX[6]	D816Y
Chantom et al[40]	United States	28	F	23	MCL, progressed from solidary mastocytoma	2004	Normal	NA
Schmid	Germany	29	F	51	SM-AHNMD (AML progressed from MDS-MPN)	2009	Normal	No D816V found
Valentini et al[39]	Italy	30	F	45	MCL		Normal	D816V
Baurmann	Germany	31	F	44	SM-AHNMD (MDS-MPN with Eos)	2003	Normal	D816V
Baurmann	Germany	32	F	49	SM-AHNMD (MDS-RCMD)	2008	Normal	D816V

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Table A1. Patient and SM Characteristics (continued)

Author*	Country	Patient No.	Sex	Patient Age at AlloHCT (years)	Diagnosis	Year of Diagnosis of Primary SM	Cytogenetic Abnormality	*KIT* Mutation
Shore		33	M	59	MCL	2008	Normal	D816V
Shore		34	M	57	SM-AHNMD (MDS)	2011	del7q	D816V
Scott	United States	35	M	35	SM-AHNMD (MDS-MPN)	2004	Normal	NA
Scott	United States	36	M	31	MCL	2004	Complex:43-44,XY,?del(3)(p?),-8,?add(9)(q34),−10,?der(11)t(8;11)(q?11.2;q?13),add(16)(q24),?del(17)(q11.2)add(19)(q13.3),add(20)(q13.3)[cp13]/46,XY[7]	No D816V found
Scott	United States	37	M	21	SM-AHNMD (AML) in CR2	2006	t(8;21)(q22;q22)	NA
Scott	United States	38	M	46	SM-AHNMD (AML) secondary to MDS	2008	NA	No D816V found
Scott	United States	39	F	43	SM-AHNMD (MDS)	2010	46,XX[30], abnormal IFISH (25.6%) for additional copy of EVI1 (3q26)	D816V
Scott	United States	40	F	31	SM-AHNMD (MDS)	2008	Normal	No D816V found
Legrand	France	41	M	62	SM-AHNMD	2008	−Y	D816V
Damaj/Yakoub-agha	France	42	F	31	ASM	2001	NA	NA
Damaj/Yakoub-agha	France	43	M	57	SM-AHNMD (MM)	1998	NA	NA
Damaj/Yakoub-agha	France	44	M	42	SM-AHNMD (ALL)	2003	NA	NA
Damaj/Yakoub-agha	France	45	M	47	ASM	2007	NA	NA
Damaj/Yakoub-agha	France	46	F	50	ASM	2002	NA	NA
Godley	United States	47	F	50	MCL	2005	del (1p), add (6q), −9, add (16p)	NA
Van Lint	Italy	48	F	36	SM-AHNMD (AML)	2002	inv16	No D816V found
Perales	United States	49	F	40	MCL	1992	NA	NA
Perales	United States	50	M	50	SM-AHNMD (MPN-MDS), SM secondary to UP	2000	Normal	NA
Perales	United States	51	F	57	SM-AHNMD (MDS RAEB), SM secondary to UP	2011	Normal	NA
Gilman	United States	52	F	13	MCL	2012	Normal	No D816V found
Vercellotti	United States	53	M	60	SM-AHNMD (MPN-MDS RAEB-I, 8% blasts)	2010	+8	D816V
Ustun	United States	54	F	64	SM-AHNMD (AML) (therapy induced)	2009	−7	NA
Nakamura	United States	55	F	36	SM-AHNMD (MPN-CMML)	2011	Normal	NA
Nakamura	United States	56	M	67	SM-AHNDM (MDS-MPN)	2011	Normal	D816V
Nakamura	United States	57	M	41	SM-AHNMD (AML, secondary to MDS)	2003	Normal	NA

Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic stem-cell transplantation; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; CR2, second complete remission; CMML, chronic myelomonocytic leukemia; Eos, eosinophilia; F, female; M, male; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasia; MML, myelomastocytic leukemia; MM, multiple myeloma; NA, not available; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RCMD, refractory cytopenia with multilineage dysplasia; SM, systemic mastocytosis; SM-AHNMD, SM with an associated clonal hematologic non–mast cell lineage disease; UP, urticaria pigmentosa.

*First author of a published article or one who provided information to this study.

Table A2. Transplantation Characteristics

Patient No.	Diagnosis	Date of First AlloHCT	Time From Primary SM Diagnosis to alloHCT (months)	CR Status of AML or MML at AlloHCT	KPS at AlloHCT (%)	Graft Type	Conditioning		Donor		
							Intensity	Regimen	Type	Age (years)	Sex
1	MCL-AML	December 2001	4	CR	NA	PBSC	MAC	Busulfan-cyclophosphamide-etoposide	NA		
2	SM-MPN-MDS	March 2001	48	NA	70	BM	MAC	Busulfan-cyclophosphamide	URD	34	F
3	SM-AML	1992	10	CR	NA	BM	MAC	Busulfan-cyclophosphamide-etoposide	NA		
4	ASM	February 2007	18	NA	70	PBSC	MAC	TBI-cyclophosphamide-cytarabine	URD	34	M
5	ASM	April 2012	21	NA	80	PBSC	RIC	FLAMSA-RIC and splenic XRT	RD	54	F
6	SM-AML	2006	4.5	Active AML	NA	PBSC	MAC	TBI-cyclophosphamide	RD		F
7	SM-MPN	2002	36	NA	NA	PBSC	RIC	Fludarabine-cyclophosphamide	RD	43	M
8	SM-MDS	2001	36	NA	NA	PBSC	RIC	Fludarabine-cyclophosphamide	RD	54	F
9	MCL	2001	60	NA	NA	PBSC	RIC	Fludarabine-cyclophosphamide	RD	52	F
10	MCL	March 2007	21	NA	90	PBSC	MAC	Busulfan-cyclophosphamide-antithymocyte globulin	URD		M
11	SM-AML	December 1996	8	CR	100	BM	MAC	TBI-etoposide	RD	42	F
12	ASM	1996	9	NA	NA	BM	MAC	Busulfan-cyclophosphamide-thiotepa	NA		
13	SM-AML	2004	9	CR	90	PBSC	MAC	FTBI-etoposide	RD	48	F
14	SM-AML	1990	2	Active AML	NA	BM	MAC	TBI-cyclophosphamide	RD		F
15	MML	July 2001	4	CR regarding myeloblasts	NA	PBSC	RIC	Fludarabine-TBI	RD		F
16	MCL	2000	Approximately 3	NA	NA	BM	MAC	Busulfan-cyclophosphamide	URD		F
17	SM-AML	March 2010	11	Active AML	80	PBSC	MAC	Busulfan-cyclophosphamide	RD	49	M
18*	MCL	May 2002	9	NA	90	BM	RIC	Fludarabine-melphalan-antithymocyte globulin	URD		
19	SM-AML	November 2011	6	CR	90	PBSC	RIC	Fludarabine-melphalan	RD	63	M
20	SM-AML	September 2011	9	CR	90	PBSC.	MAC	TBI-cyclophosphamide	URD	30	M
21	ASM	July 2006	60	NA	50	PBSC	RIC	Fludarabine-melphalan-thiotepa	URD	22	M
22*	SM-AML	August 2012	84	CR	80	PBSC	RIC	FLAMSA-RIC	URD	23	F
23	SM-MDS	September 2008	13	NA	80	BM	MAC	Busulfan-cyclophosphamide-antithymocyte globulin	URD	48	M
24	SM-AML	April 2011	7	Relapse/active AML	90	PBSC	RIC	FLAMSA-RIC	RD	63	F
25	SM-AML	January 2010	26	Active AML	80	BM	MAC		RD		F
26	SM-AML	June 2008	72	CR (CRi)	90	PBSC	MAC	Tresulfan-fludarabine	URD	41	M
27*	MCL	May 2012	11	NA	100	UCB	MAC	Fludarabine-cyclophosphamide-TBI	UCB		M
28	MCL	October 2004	216	NA	90	PBSC	MAC	Fludarabine-busulfan	RD	21	F

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Table A2. Transplantation Characteristics (continued)

Patient No.	Diagnosis	Date of First AlloHCT	Time From Primary SM Diagnosis to alloHCT (months)	CR Status of AML or MML at AlloHCT	KPS at AlloHCT (%)	Graft Type	Conditioning		Donor		
							Intensity	Regimen	Type	Age (years)	Sex
29	SM-AML	March 2011	13	CR (CRi)	90	PBSC	RIC	FLAMSA-RIC	RD	46	F
30	MCL	January 2005	21	NA	70	PBSC	MAC	Busulfan-cyclophosphamide	RD	41	F
31	SM-MDS-MPN	September 2007	17	NA	90	PBSC	MAC	TBI-fludarabine -cyclophosphamide-antithymocyte globulin	RD	46	F
32*	SM-MDS	September 2010	85	NA	100	BM	MAC	Thiotepa-busulfan-cyclophosphamide-antithymocyte globulin	URD		F
33	MCL	March 2009	7	NA	80	PBSC	MAC	Fludarabine-busulfan-antithymocyte globulin	URD		M
34	SM-MDS	May 2012	5	NA	90	BM	MAC	Fludarabine-melphalan	URD	45	M
35	SM-MDS-MPN	October 2000	8	NA	NA	PBSC	MAC	Busulfan-cyclophosphamide	RD	33	F
36	MCL	February 2005	8	NA	NA	PBSC	MAC	Fludarabine-busulfan	URD	21	M
37	SM-AML	February 2005	12	CR2	NA	PBSC	MAC	TBI-cyclophosphamide	RD	25	M
38	SM-AML	February 2007	5	CR	NA	PBSC	RIC	TBI-fludarabine	URD	40	M
39	SM-MDS	February 2009	10	NA	80	PBSC	MAC	Busulfan-cyclophosphamide	URD	41	M
40	SM-MDS	February 2011	5	NA	90	BM	MAC	TBI-cyclophosphamide	RD	26	F
41	SM-MPN	January 2009	5	NA	70	BM	RIC	Fludarabine-melphalan	RD	63	F
42	ASM	November 2009	65	NA	NA	BM	MAC	Busulfan-cyclophosphamide	RD	29	M
43	SM-MM	February 2003	18	NA	NA	PBSC	RIC	Busulfan-fludarabine-antithymocyte globulin	RD	39	F
44	SM-ALL	January 1999	5	NA	NA	BM	MAC	TBI-cyclophosphamide	RD	38	M
45	ASM	June 2005	19	NA	NA	PBSC	RIC		RD		M
46	ASM	November 2007	7	NA	NA	PBSC	RIC	Fludarabine-busulfan	RD		M
47	MCL	August 2002	5	NA	90	PBSC	RIC	Fludarabine-melphalan-alemtuzumab	RD		F
48	SM-ASM-AML	October 2005	8	Active AML	60	BM	MAC	TBI-cyclophosphamide	RD	44	M
49	MCL	June 2003	8.5	NA	70	PBSC	MAC	TBI-thiotepa-fludarabine	RD	37	M
50	SM-MPN-MDS	November 2000	96	NA	80			TBI-thiotepa-fludarabine	RD	45	M
51	SM-MDS	February 2003	32	NA	NA	BM	MAC	Busulfan-melphalan	RD	53	F
52	MCL	July 2011	5	NA	80	PBSC	MAC	TBI-thiotepa-fludarabine-antithymocyte globulin-local radiation to vertebrae	Haploidentical (mother)	42	F
53	SM-MPN-MDS	May 2013	5	NA	90	PBSC	RIC	TBI-cyclophosphamide-fludarabine	RD	62	F
54*	SM-AML	February 2011	3	CR	90	UCB	RIC	TBI-cyclophosphamide-fludarabine	UCB		
55	SM-CMML	January 2010	4	NA	90	PBSC	MAC	Fludarabine-melphalan-TMI	RD	36	M
56	SM-AML (MDS-MPN)	December 2011	8	NA	90	PBSC	RIC	Fludarabine-melphalan	RD	65	F
57	SM-AML secondary to MDS?)	December 2011	3	CR	90	PBSC	RIC	Fludarabine-melphalan	URD	44	M

Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic stem-cell transplantation; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CR2, second complete remission; Cri, complete remission with incomplete blood recovery; F, female; FLAMSA-RIC, fludarabine, amsacrine, cytarabine-antithymocite globulin, cyclophosphamide, busulphan or TBI; FTBI, fractionated total body irradiation; KPS, Karnofsky performance status; M, male; MAC, myeloablative conditioning; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MML, myelomastocytic leukemia; MPN, myeloproliferative neoplasia; NA, not available or not applicable; PBSC, peripheral blood stem cell; RD, related donor; RIC, reduced-intensity conditioning; SM, systemic mastocytosis; TBI, total body irradiation; TMI, total marrow irradiation; UCB, umbilical cord blood; URD, unrelated donor; XRT, external radiation therapy.

*HLA-mismatched alloHCTs.

Table A3. Response in SM and Survival After First AlloHCT

Patient No.	Disease	Reference	Serum Tryptase (ng/mL)			Percentage of Mast Cells in BM*			Other SM-Related Changes After AlloHCT	SM Response to First AlloHCT	Progression of SM After Initial Response		Treatment After AlloHCT and Response	Alive (yes/no)	Time From First AlloHCT (months)	Cause of Death
			At Diagnosis	At AlloHCT	After AlloHCT	At Diagnosis	At AlloHCT	After AlloHCT			Yes/No	Time				
1	MCL-AML	Chen et al[36]				40	27.5	40 at 1 month	Hepatomegaly, splenomegaly, and pancytopenia persisted	SD	No			Yes	12	
2	SM-MPN					↑	↑ ↑	0 at 3 months	Eosinophil infiltrate (44%) in BM resolved (5%); dyserythropoiesis resolved	R	No			No	4	Infection and MOF
3	SM-AML	Födinger et al[29]				↑	4	5 at 3 months		SD	No			Yes	60	
4	ASM			> 200	189 at 3 months		75	30 at 3 months		R	No			No	3	CNS bleeding
5	ASM					0		0 at 1 month	Improvement in spleen and liver size	R	Yes	At 7 months	Cladribine, steroids, DLI: P	No	12	Progression of SM
6	SM-AML	Nagai et al[35]				5	7	↑ ↑ at 6 months		P			No treatment	Yes	12	
7	SM-MPN	Nakamura et al[37]		889	404 at 6 months				Eosinophilia decreased (15×10^9/L to 0.6×10^9/L	R	Yes	At 6 months	DLI	Yes	9	
8	SM-MDS	Nakamura et al[37]		150	60 at 10 months	↑ ↑		↑	Episodic hot flashes and syncope resolved	R	No		DLI†	Yes	39	
9	MCL	Nakamura et al[37]		> 200	↑ ↑				Hepatosplenomegaly and pancytopenia worsened	P			No treatment	No	5	Progression of SM
10	MCL			333	95 at 2 months		5	1.5 at 2 months		R	No			No	3	Sepsis
11	SM-AML				7		5	5 at 3 months		SD	No			Yes	206	
12	ASM	Przepiorka et al[30]					30	0 at 1 month	Splenomegaly resolved	R (CR)	No			Yes	24	
13	SM-AML	Pullarkat et al[33]			17.4		90	0 at 10 months		R (CR)	No			Yes	108	
14	SM-AML	Rønnov-Jessen et al[32]				↑		↑	Liver infiltration persisted	SD				Yes	8	
15	MML	Sperr et al[28]	745	126	73 at 2 months	10	5	5 at 2 months		SD	Yes	At 3 months	Second alloHCT after MAC: CR	Yes	144	
16	MCL	Spyridonidis et al[34]				70 by morphology	14 by flow	5 at 1 month; 2.4 by flow at 12 months	Urine histamine level was normalized	R	No		DLI†	Yes	44	
17	SM-AML		97	69	27 at 3 months	5-10	> 10	1 at 3 months	Mediator-related symptoms resolved, skin lesions improved	R	No			Yes	30	
18	MCL					90	30	0 at 1 month		R (CR)	No			No	2	Sepsis
19	SM-AML		71			10	10	10 at 3 months		SD	No			Yes	16	
20	SM-AML		542	291		30	30	5 at 7 months		R	No			Yes	18	
21	ASM			136	142 at 1 month		80	50 at 1 month		SD	Yes	At 3 months	Dasatinib: P	No	10	Progression of SM
22	SM-AML		230	34	19 at 4 months		< 10	0 at 4 months	Improvement in liver, skin, and lymph nodes	R (CR)	No			Yes	11	
23	SM-MDS		530	200	9.6 at 3 months	50	5	5 at 3 months	Improvement in liver and skin	R	Yes	At 24 months	DLI: SD; second alloHCT with RIC: CR	Yes	52	

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Table A3. Response in SM and Survival After First AlloHCT(continued)

Patient No.	Disease	Reference	Serum Tryptase (ng/mL)			Percentage of Mast Cells in BM*			Other SM-Related Changes After AlloHCT	SM Response to First AlloHCT	Progression of SM After Initial Response		Treatment After AlloHCT and Response	Alive (yes/no)	Time From First AlloHCT (months)	Cause of Death
			At Diagnosis	At AlloHCT	After AlloHCT	At Diagnosis	At AlloHCT	After AlloHCT			Yes/No	Time				
24	SM-AML		875	114	22 at 1 month	35	10	< 5 at 1 month	Improvement in liver function tests	R	No		Second alloHCT with RIC for AML†:CR	Yes	21	
25	SM-AML		349		15 at 3 months	60	10	0	Improvement in bone, spleen, and liver	R	No			No	11	AML relapse
26	SM-AML	Pardanani et al[20]		90	< 11 at 36 months	70	78	0 at 1 month	Improvement in nodes, spleen, and liver	R (CR)	No			Yes	42	
27	MCL		496	15		99	40	3 at 2 months	Improvement in skin, spleen, and liver; cytogenetic remission	R	Yes	At 4 months	No treatment	No	4	Progression of SM
28	MCL	Chantorn et al[40]	> 200			5; then 79 (MCL)	60	80 at 1 month	Mediator-related symptoms persisted	P			No treatment	No	4	Progression of SM
29	SM-AML		37	38	20 at 3 months	15			Improvement in skin, splenomegaly persisted	SD	Yes	At 3 months	Cladribine	No	6	Graft failure-sepsis
30	MCL	Valentini et al[39]	> 200	35		90	10	1.5 at 1 month		R	No			No	1	Traffic accident
31	SM-MDS-MPN		216	145	9 at 24 months	5	< 5	0 at 24 months	Splenomegaly resolved; KIT^{D816V} became undetectable in BM cells	R (CR)	No		DLI†	Yes	72	
32	SM-MDS		61	48	14 at 34 months	80	35	4 at 34 months	Severe myelofibrosis improved	R	No		DLI†	Yes	34	
33	MCL		535			70	70	10 at 3 months		R	No			No	8	Respiratory failure
34	SM-MDS		> 400	25	2.1 at 12 months	80	20	0 at 12 months		R (CR)	No		TKI†, DLI†	yes	12	
35	SM-MDS-MPN						20-25	0 at 1 month	Splenomegaly persisted	R	No			No	7	Severe GVHD
36	MCL		1,500				90	50 at 1 month	Splenomegaly worsened	P				No	1	Progression of SM
37	SM-AML				26		25	1 at 2 months		R	No			Yes	68	
38	SM-AML		110				4	0.1 at 2 months		R	No		DLI†,TKI†	No	9	AML relapse
39	SM-MDS		919	11.3	6.2 at 3 months	40	2-3	2 at 12 months		SD	No			Yes	28	
40	SM-MDS		820	394	4.4 at 12 months		20	0 at 1 month		R (CR)	No			Yes	19	
41	SM-AHNMD		230	200	9 at 3 months	30	30	0 at 3 months	No evidence of mast cells in liver and GI tract biopsies; KIT^{D816V} became undetectable in the BM cells; diarrhea resolved	R (CR)	No			No	30	Pulmonary fibrosis

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Table A3. Response in SM and Survival After First AlloHCT (continued)

Patient No.	Disease	Reference	Serum Tryptase (ng/mL)			Percentage of Mast Cells in BM*			Other SM-Related Changes After AlloHCT	SM Response to First AlloHCT	Progression of SM After Initial Response		Treatment After AlloHCT and Response	Alive (yes/no)	Time From First AlloHCT (months)	Cause of Death
			At Diagnosis	At AlloHCT	After AlloHCT	At Diagnosis	At AlloHCT	After AlloHCT			Yes/No	Time				
42	ASM		230							R (CR)	No			Yes	27	
43	SM-MM									SD	No			Yes	105	
44	SM-ALL									R (CR)	No			Yes	56	
45	ASM		250							P				No	6	Progression of SM
46	ASM									R (CR)	No			Yes	30	
47	MCL					95	90	0 at 3 months		R (CR)	Yes	At 12 months		No	15	Progression of SM
48	SM-AML					15	15	< 5 at 4 months		R	Yes	At 12 months	DLI	No	12	Progression of SM and AML
49	MCL					38	10	0 at 12 months	Mast cells persisted in liver biopsy	R	No		DLI†	Yes	82	
50	SM-MDS-MPN					Present	Some mast cells	< 5 at 36 months	Eosinophils significantly decreased in BM	R	No		DLI†	Yes	150	
51	SM-MDS						Rare	Rare-scattered		SD	No			Yes	104	
52	MCL		> 1,200	63	3 at 1 month	80	10	0 at 1 month		R (CR)	Yes	At 1 month	DLI	No	2	Progression of SM
53	SM-MDS-MPN		49	45	37 at 1 month		5	5 at 1 month		SD	No			Yes	3	
54	SM-AML						5	0 at 3 months		R (CR)	No			No	5	AML relapse
55	SM-MPN		69.4	67	5 at 3 months	5		0 at 3 months	Hepatosplenomegaly resolved	R (CR)	No			Yes	33	
56	SM-MDS-MPN		> 400	> 400	16 at 3 months	15-20	30	0 at 3 months	Ascites continued	R	No			No	10	GVHD-sepsis
57	SM-AML			145	9 at 1 month	5	50	0 at 1 month	Hepatosplenomegaly persisted	R	No			No	14	AML relapse

Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic stem-cell transplantation; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; BM, bone marrow; CR, complete remission; DLI, donor leukocyte infusion; GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MML, myelomastocytic leukemia; MOF, multiple organ failure; MPN, myeloproliferative neoplasia; P, progression; R, response; RD, related donor; RIC, reduced-intensity conditioning; SD, stable disease; SM, systemic mastocytosis; SM-AHNMD, SM with an associated clonal hematologic non–mast cell lineage disease; TKI, tyrosine kinase inhibitor.

*Earliest time point when best response occurred after first alloHCT.

†Treatment given for SM stable disease, graft failure, mixed chimerism, or progression in hematologic malignancy but not for SM progression.