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Secondary Acute Myeloid Leukemia and the Role of Allogeneic Stem Cell Transplantation in a Population-Based Setting

Christer Nilsson[1,*], Erik Hulegårdh[2], Hege Garelius[2], Lars Möllgård[2], Mats Brune[2], Anders Wahlin[3], Stig Lenhoff[4], Ulla Frödin[5], Mats Remberger[6], Martin Höglund[8], Gunnar Juliusson[4], Dick Stockelberg[7], Sören Lehmann[1,8]

[1] *Division of Hematology, Department of Medicine, Karolinska Institute, Stockholm, Sweden*
[2] *Section of Hematology and Coagulation, Department of Medicine, Sahlgrenska University Hospital, Göteborg, Sweden*
[3] *Department of Radiation Sciences, University of Umeå, Umeå, Sweden*
[4] *Department of Hematology, Skåne University Hospital, Lund University, Lund, Sweden*
[5] *Departments of Hematology and Medical and Health Sciences, Linköping University, Linköping, Sweden*
[6] *Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden*
[7] *Department of Medicine and Oncology, Södra Älvsborgs Hospital, Borås, Sweden*
[8] *Department of Medical Sciences, Uppsala University, Uppsala, Sweden*

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A B S T R A C T

Secondary AML (s-AML), including AML with an antecedent hematologic disorder (AHD-AML) and therapy-related AML (t-AML), constitutes a large proportion of patients with AML and is considered to confer a dismal prognosis. The role of allogeneic hematopoietic cell transplantation (HCT) in patients with s-AML and the extent to which HCT is performed in these patients has been little studied to date. We used the population-based Swedish AML Registry comprising 3337 intensively treated adult patients over a 17-year period to study the role of HCT within the group of patients with s-AML as well as compared with patients with de novo AML. HCT was performed in 576 patients (22%) with de novo AML, in 74 patients (17%) with AHD-AML, and in 57 patients (20%) with t-AML. At 5 years after diagnosis, there were no survivors among patients with previous myeloproliferative neoplasms who did not undergo HCT, and corresponding survival for patients with antecedent myelodysplastic syndromes and t-AML was and 2% and 4%, respectively. HCT was compared with chemotherapy consolidation in s-AML using 3 models: (1) a 200-day landmark analysis, in which HCT was favorable compared with conventional consolidation ($P = .04$, log-rank test); (2) a multivariable Cox regression with HCT as a time-dependent variable, in which the hazard ratio for mortality was 0.73 (95% confidence interval, 0.64 to 0.83) for HCT and favored HCT in all subgroups; and (3) a propensity score matching analysis, in which the 5-year overall survival (OS) and relapse-free survival in patients with s-AML in first complete remission (CR1) was 48% and 43%, respectively, for patients undergoing HCT versus 20% and 21%, respectively, for those receiving chemotherapy consolidation ($P = .01$ and .02, respectively, log-rank test). Our observational data suggest that HCT improves survival and offers the only realistic curative treatment option in patients with s-AML.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the most potent postremission therapy in patients with acute myeloid leukemia (AML) [1,2], and is widely used in younger patients with intermediate-risk or adverse-risk cytogenetics [3]. Transplantation decisions are based mainly on cytogenetic and molecular risk group, age, comorbidity, response to therapy, and the availability of a suitable donor [4]. AML is secondary (s-AML) in more than 25% of all cases, arising after previous chemotherapy and/or radiotherapy (i.e., therapy-related [t-AML]) or developing after an antecedent myeloid disease (AHD-AML), such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN). s-AML has been identified as an independent predictor of poor outcome [5], especially in non-MDS s-AML [6], but is not included in the current risk classifications that provide the basis for decisions regarding HCT, such as the European LeukemiaNet (ELN) criteria [7]. Nevertheless, patients with s-AML may be considered for HCT, which has proven to be an effective treatment for these patients [8–11]. The extent to which HCT is performed in this patient

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* Correspondence and reprint requests: Christer Nilsson, MD, PO Hematologi, M54, Karolinska Universitetssjukhuset, Huddinge, 141 86 Stockholm, Sweden.
E-mail address: christer.nilsson@ki.se (C. Nilsson).

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group, and how HCT influences survival in this group, have not yet been fully elucidated, however.

Here we used Swedish national population-based registries encompassing all patients with AML diagnosed between 1997 and 2013 to characterize the extent to which HCT is performed and to evaluate the impact of HCT in a real-life setting. Our main aim was to explore these issues in patients with s-AML and also in the context of the entire cohort of patients with AML undergoing HCT, including patients with de novo AML in the analysis.

METHODS

Study Population and Study Design

We used data from 2 nationwide registries: the Swedish AML Registry [12] and the Swedish Cancer Registry. Reporting to the Swedish Cancer Registry is mandatory for both treating clinicians and pathologists. The overlap between these 2 registries is 98%, indicating that our study involves a true population-based sample [13]. Patient characteristics, diagnostic findings, and management, including treatments and outcomes, were retrieved from the AML registry. All patients in the AML registry where then validated in the Swedish Cancer Registry, and preceding malignant diagnoses in cases of s-AML were also identified through the Swedish Cancer Registry. Additional detailed transplantation data for patients with s-AML who underwent HCT were retrieved from all 6 centers in Sweden performing HCT through a search of their medical records or collected from local registries. Patients with acute promyelocytic leukemia (APL) were excluded. Survival data were updated from the Swedish Population Registry in May 2014. The Regional Ethical Board of Gothenburg approved the study (EPN 503-11, EPN 781-13).

All intensively treated patients received induction therapy with cytarabine and daunorubicin according to Swedish guidelines published in 2006 [14] at the specified dose of 1 g/m^2 cytosine arabinoside twice daily on days 1 to 5 and daunorubicin 60 mg/m^2 on days 1 to 3. Before 2006, both cytarabine and daunorubicin were administered at varying doses based on local guidelines, but always at doses equivalent to those in a classical intensive AML induction course. Consolidation treatment consisted of 1 to 3 courses of combination therapy including intermediate-dose or high-dose Ara-C followed by HCT in eligible patients.

We first analyzed all patients treated with HCT and chemotherapy consolidation, defining their crude overall survival (OS). Thereafter, we limited our cohort to patients with unfavorable-risk cytogenetics age ≤65 years and in CR1. In this patient group, we evaluated the impact of HCT using both a landmark analysis and a time-dependent multivariable Cox regression analysis in both patients with de novo AML and those with s-AML. Furthermore, in patients with s-AML, we compared HCT versus chemotherapy using propensity score matching. Finally, we evaluated possible factors influencing survival after HCT in patients with s-AML. An outline of the study design, with numbers of included patients in the different analyses, is shown in Figure 1.

Definitions

AHD-AML was defined as AML with a previous diagnosis of a myeloid hematologic disease known to confer an increased risk of transformation to AML, including MDS (MDS-AML) and MPN (MPN-AML). t-AML was defined as AML with a previous diagnosis of a malignant or nonmalignant disease that had been treated with cytotoxic and/or radiation therapy. All previous chemotherapy regimens were considered, including methotrexate and cyclophosphamide for rheumatic disease. Immunosuppressive treatment using nonchemotherapeutic agents was not considered cytotoxic. Patients developing MDS or MPN in the interval between the chemotherapy or radiation treatment for their primary disease and the diagnosis of AML were classified as having t-AML. Similarly, patients treated with chemotherapy or radiation for their MPN or MDS were classified as having AHD-AML. Cytogenetic risk was defined according to the 2010 ELN criteria [15], with consideration of mutational status starting in 2011. The definition of CR was <5% blasts in the bone marrow on morphological evaluation and recovery of peripheral blood counts.

Statistical Analyses

Continuous variables were compared using the Mann-Whitney *U* test, and the Pearson's chi-square test was used for categorical data. The median duration of follow-up was calculated by the reverse Kaplan-Meier method using the R *prodlim* package [16,17]. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. A day 200 landmark approach was used to reduce immortal time bias [18,19]. The Cox proportional hazard model was used for multivariable analyses, with HCT as a time-dependent variable, using the R *survival* package [20]. Age, the sole continuous variable, was dichotomized owing to nonlinearity and was included as a stratum variable, because it did not fulfill the proportional hazards assumption, which was

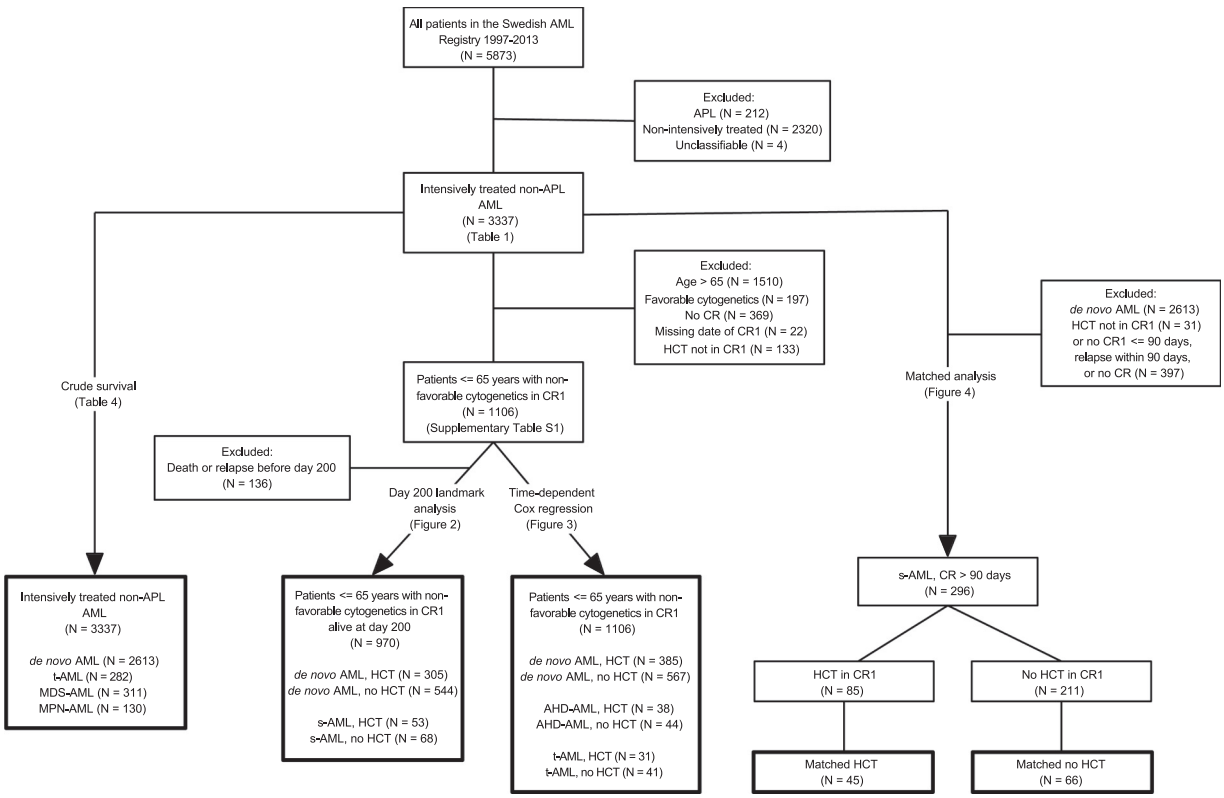

Figure 1. CONSORT diagram showing the study cohort and inclusions/exclusions for the analyses performed.

Table 1
Characteristics of the 3337 Intensively Treated Patients with AML (APL Excluded) in Sweden between 1997 and 2013

Characteristic		t-AML	AHD-AML	de novo AML	*P* Value
Number		282	442	2613	
Sex, n (%)	Male	121 (43)	275 (62)	1387 (53)	<.001
	Female	161 (57)	167 (38)	1226 (47)	
Age, yr, median (range)		65 (18-89)	68 (24-86)	63 (17-88)	<.001
ECOG ps, n (%)	0-1	212 (79)	321 (76)	1939 (78)	.556
	2-4	57 (21)	102 (24)	544 (22)	
Cytogenetic risk, n (%)	Adverse	105 (45)	164 (46)	633 (28)	<.001
	Intermediate	109 (47)	179 (51)	1370 (61)	
	Favorable	20 (9)	11 (3)	240 (11)	
WBC, mean (SD)		23.9 (38.5)	25.7 (42.4)	37.5 (57.0)	.001
CR, n (%)		169 (60)	199 (45)	1894 (72)	<.001
HCT disease status, n (%)	CR1	45 (16)	55 (12)	425 (16)	<.001
	Not performed	225 (80)	368 (83)	2037 (78)	
	Primary refractory	2 (1)	12 (3)	21 (1)	
	Relapse	10 (4)	7 (2)	130 (5)	

Percentages of overall cases with values not reported: ECOG ps, 5%; cytogenetic risk, 15%; WBC, 56%.
ECOG ps, Eastern Cooperative Oncology Group Performance Status.

tested using the scaled Schoenfeld residuals for all variables. Propensity score matching analysis was performed using the R *MatchIt* package [21] with nearest-neighbor matching and a caliper of 0.25 SD on continuous variables and an exact match on categorical variables. Matching criteria were the type of s-AML (AHD- or t-AML), cytogenetic risk group, age, and year of diagnosis. The cumulative incidence of relapse was calculated considering competing risks using the R *cmprsk* package [22,23]. Analysis of factors associated with survival after HCT was performed with univariable and multivariable Cox proportional hazards models. In models including graft-versus-host disease (GVHD), patients who did not survive for >100 days were excluded. Two-sided *P* values with a significance level of .05 were used in all analyses. *P* values were not adjusted for multiple testing. Statistical analyses were performed using R version 3.4.3 [24].

RESULTS

Study Population and General Characteristics

The study population comprised all 5873 adult patients diagnosed with AML during the 17-year period 1997 to 2013 (Figure 1). Only the 3337 patients with non-APL AML who received intensive induction therapy were included for further analyses. In these patients, the median duration of follow-up from the date of diagnosis was 95 months (interquartile range, 48 to 147 months). Seven patients were lost to follow-up. Patient characteristics are summarized in Table 1. Of these patients, 2613 (78%) had de novo AML, 282 (8%) had t-AML, and 442 (13%) had AHD-AML, including 130 (4%) with MPN-AML and 311 (9%) with MDS-AML. The median age at diagnosis was 68 years in the patients with AHD-AML, 65 years in those with t-AML, and 63 years in those with de novo AML ($P < .001$, AHD-AML versus de novo; $P = .041$, t-AML versus de novo). There was a male preponderance in the de novo AML group (53%) and the AHD-AML group (62%; $P < .001$), and a female preponderance in the t-AML group (57%; $P = .001$). Patients with de novo AML were more likely to achieve CR: 72%, compared with 60% in the t-AML group and 45% in the AHD-AML group ($P < .001$ for both t-AML and AHD-AML versus de novo AML).

Characteristics of Patients with s-AML Who Underwent HCT

Of the 3337 intensively treated patients, 707 (21%) underwent HCT at any stage of AML. HCT was performed in 576 patients (22%) in the de novo AML group, 74 patients (17%) in the AHD-AML group, and 57 patients (20%) in the t-AML group. One hundred (76%) patients with s-AML underwent HCT in CR1, including 55 patients (74%) with AHD-AML and 45 (79%) with t-AML. The remaining patients underwent HCT while in refractory or relapsed status or in later CR. The proportion of patients in CR1 who

Table 2
Characteristics of Patients in CR1 Consolidated with HCT and Those Not Consolidated with HCT by AML Subgroup

Characteristic		t-AML			AHD-AML			de novo AML		
		HCT	No HCT	*P* Value	HCT	No HCT	*P* Value	HCT	No HCT	*P* Value
Number		45	122		55	141		425	1452	
Sex, n (%)	Male	17 (38)	52 (43)	.699	30 (55)	83 (59)	.697	209 (49)	749 (52)	.414
	Female	28 (62)	70 (57)		25 (45)	58 (41)		216 (51)	703 (48)	
Age, yr, median (range)		51 (18-68)	66 (34-83)	<.001	58 (28-77)	68 (24-83)	<.001	48 (17-72)	64 (17-86)	<.001
ECOG ps, n (%)	0-1	41 (93)	103 (87)	.435	50 (93)	112 (82)	.117	358 (87)	1119 (80)	.001
	2-4	3 (7)	15 (13)		4 (7)	24 (18)		53 (13)	280 (20)	
Cytogenetic risk, n (%)	Adverse	22 (50)	29 (30)	.060	25 (50)	45 (37)	.166	137 (35)	257 (20)	<.001
	Intermediate	17 (39)	56 (57)		22 (44)	72 (60)		236 (61)	816 (65)	
	Favorable	5 (11)	13 (13)		3 (6)	4 (3)		14 (4)	187 (15)	
WBC, mean (SD)		19.4 (31.9)	17.5 (29.4)	.778	19.2 (31.0)	19.8 (26.1)	.926	41.2 (60.8)	34.8 (55.3)	.164

Percentages of overall cases with values not reported in t-AML: ECOG ps, 3%; cytogenetic risk, 15%; WBC, 47%; in AHD-AML: ECOG ps, 3%; cytogenetic risk, 14%; WBC, 51%; in de novo AML: ECOG ps, 4%; cytogenetic risk, 12%; WBC, 57%.

Table 3
Characteristics of Patients with Secondary AML Who Underwent Allogeneic HCT in First Remission

Characteristic		s-AML overall	AHD-AML	t-AML	*P* Value
Number of patients		100	55	45	
Time period of HCT, n (%)	1997-2004	24 (24)	16 (29)	8 (18)	.279
	2005-2014	76 (76)	39 (71)	37 (82)	
Age, yr, median (range)		54 (18-77)	58 (28-77)	51 (18-68)	.002
Sex, n (%)	Male	47 (47)	30 (55)	17 (38)	.142
	Female	53 (53)	25 (45)	28 (62)	
Secondary type, n (%)	MDS-AML	42 (42)	42 (76)	0 (0)	<.001
	MPN-AML	13 (13)	13 (24)	0 (0)	
	t-AML	45 (45)	0 (0)	45 (100)	
Cytogenetic risk, n (%)	Intermediate	39 (41)	22 (44)	17 (39)	.621
	Adverse	47 (50)	25 (50)	22 (50)	
	Favorable	8 (9)	3 (6)	5 (11)	
Donor type, n (%)	RD	38 (39)	20 (38)	18 (40)	.983
	URD	60 (61)	33 (62)	27 (60)	
Conditioning, n (%)	Myeloablative	35 (37)	15 (29)	20 (47)	.118
	Nonmyeloablative	60 (63)	37 (71)	23 (53)	
Donor age, yr, median (range)		37 (19-72)	36 (19-72)	38 (20-70)	.807
Stem cell source, n (%)	BM	11 (11)	6 (11)	5 (11)	1.000
	MBP	86 (89)	47 (89)	39 (89)	
Female donor-male recipient, n (%)		10 (11)	6 (12)	4 (9)	.986
EBMT score, n (%)	≤3	47 (87)	27 (84)	20 (91)	.772
	>3	7 (13)	5 (16)	2 (9)	
HCT-CI score, n (%)	>2	24 (43)	10 (30)	14 (61)	.046
	0-2	32 (57)	23 (70)	9 (39)	
Interval from CR1 to HCT, d, n (%)	<94.5	42 (50)	21 (47)	21 (54)	.662
	>94.5	42 (50)	24 (53)	18 (46)	
Acute GVHD, n (%)	0-1	62 (66)	29 (56)	33 (79)	.036
	2-4	32 (34)	23 (44)	9 (21)	
Chronic GVHD, n (%)	None	41 (51)	20 (49)	21 (54)	.799
	Mild	20 (25)	10 (24)	10 (26)	
	Moderate/severe	19 (24)	11 (27)	8 (21)	
CMV reactivation, n (%)	Yes	42 (46)	21 (40)	21 (52)	.344

The median time from CR1 to HCT was 94.5 days. Percentages of cases with values not reported: cytogenetic risk, 6%; donor type, 2%; conditioning, 5%; donor age, 10%; stem cell source, 3%; donor sex, 5%; EBMT score, 46%; HCT-CI score, 44%; exact date of CR1 or HCT, 16%, acute GVHD, 6%; chronic GVHD, 20%; CMV reactivation, 8%.
RD indicates related donor; URD, unrelated donor; BM, bone marrow; MBP, mobilized peripheral blood; EBMT, European Society for Blood and Marrow Transplantation; HCT-CI, Hematopoietic Cell Transplantation Specific-Comorbidity Index; CMV, cytomegalovirus.

underwent HCT in first remission was similar in the de novo AML, AHD-AML, and t-AML groups: 23%, 28%, and 27%, respectively. Characteristics of the patients in CR1 are reported in Table 2. The median patient age at HCT was significantly higher in the AHD-AML group compared with the de novo AML and t-AML groups (58 years versus 48 years versus 51 years, respectively; $P < .001$, AHD-AML versus de novo AML; $P = .23$, t-AML versus de novo AML). The cytogenetic risk profile for HCT recipients differed among the groups; intermediate-risk patients were predominant in the de novo AML group, and adverse risk was the most common cytogenetic risk group in the AHD-AML and t-AML groups, constituting one-half of the patients (Table 2). In general, favorable-risk patients were more common in the de novo AML group compared with the s-AML group (11% versus 5%).

Characteristics of patients with s-AML who underwent allogeneic HCT in CR1 are shown in Table 3. Among these patients, 39% received a graft from a related donor and 61% received a graft from an unrelated donor, and 37% received a myeloablative conditioning regimen and 63% received a nonmyeloablative regimen. The stem cell source was peripheral blood in 89% of the patients. There was no significant difference between the AHD-AML and t-AML groups in terms of donor type, conditioning regimen, stem cell source, female donor to male recipient, European Society for Blood and Marrow Transplantation score [25], or time from CR1 to HCT. The proportion of Hematopoietic Cell Transplantation-Specific Comorbidity Index [26] scores >2 was higher in the t-AML group compared with the AHD-AML group (61% versus 30%; $P = .046$).

Crude Survival of Patients Who Underwent HCT and Those Who Did Not Undergo HCT

We first aimed to assess real-world data on crude survival in the patients with s-AML (Table 4). At 5 years after diagnosis, survival in patients who had not undergone HCT was 0% in those with MPN-AML, 2% in those with MDS-AML, and 4% in those with t-AML. Thus, in intensively treated patients with s-AML, there is virtually no long-term survival without HCT. A direct comparison of survival rates from the time of diagnosis or time of achieving CR1 between patients undergoing HCT and those not undergoing HCT at a later time point is misleading, owing to immortal time bias [19,27]; nonetheless, we can

Table 4
OS in Intensively Treated Patients Who Underwent HCT and Those Who Did Not Undergo HCT (Regardless of Disease State) at 3 Years and 5 Years after Diagnosis in Each Subtype of AML

Subtype	HCT			No HCT		
	Total Patients	OS after 3 yr, n (%)	OS after 5 yr, n (%)	Total Patients	OS after 3 yr, n (%)	OS after 5 yr, n (%)
de novo AML	576	317 (55)	231 (40)	2037	499 (24)	332 (16)
t-AML	57	24 (42)	14 (25)	225	21 (9)	10 (4)
MDS-AML	55	17 (31)	10 (18)	256	14 (5)	5 (2)
MPN-AML	19	7 (37)	6 (32)	111	3 (3)	0 (0)

conclude that the large majority of patients with s-AML who are long-term survivors had undergone HCT. The 5-year survival in these patients who underwent HCT at any time point or disease stage was 32% for those with AHD-AML, 18% for those with MDS-AML, and 25% for those with t-AML.

Crude comparisons of survival between patients with de novo AML and those with s-AML who achieved CR1 are presented as Kaplan-Meier curves in Supplementary Figures S1 and S2. s-AML was associated with significantly worse outcomes both in patients undergoing HCT in CR1 and in patients who achieved CR1 but did not undergo HCT in CR1 ($P = .005$ and $P < .001$, respectively, log-rank test).

Landmark Analysis Comparing HCT and Chemotherapy Consolidation

We further investigated whether patients with s-AML benefited from HCT through several approaches. First, we selected patients age ≤65 years who achieved CR1 and excluded patients with a favorable karyotype (characteristics presented in Supplementary Table S1) and performed a landmark analysis to reduce immortal time bias. Follow-up started at day 200 after diagnosis, excluding any early outcomes to allow for a fairer comparison of those surviving long enough to have been considered for HCT and those who actually underwent HCT. Patients who died, relapsed, or were lost to follow-up before the landmark time were excluded. The remaining patients were separated into 2 groups; patients who underwent HCT before day 200 were assigned to the HCT group, and those who had not undergone HCT by day 200 (or never underwent HCT) were assigned to the non-HCT group. For comparison, we also studied patients with de novo AML as a separate group. The analysis favored HCT in both the de novo AML and s-AML groups ($P < .001$ and $P = .04$, respectively, log-rank test) (Figure 2). In patients with s-AML, OS at 5 years post-landmark was 29% in those who received postremission therapy without HCT, compared with 52% in those who underwent HCT. These percentages were 49% and 65%, respectively, in patients with de novo AML. To test for sensitivity, a landmark of 300 days after diagnosis was chosen as another arbitrary cutoff, which yielded similar results, with significant differences between the HCT and non-HCT groups in patients with de novo AML and those with s-AML alike (Supplementary Figure S3).

Multivariable Analysis Comparing HCT with Chemotherapy Consolidation

In the same patient group (ie, patients age ≤65 with unfavorable-risk cytogenetics who achieved CR1), a multivariable Cox regression analysis with HCT as a time-dependent variable and adjusted for the subtype of AML, cytogenetic risk, and sex (with age included as a stratum variable) showed an overall hazard ratio of mortality of 0.73 (95% confidence interval, 0.64 to 0.83) associated with HCT. Additional independent factors for survival were AML subtype and cytogenetic risk (Figure 3A). The impact of HCT on survival in by subgroup in patients with s-AML is shown in Figure 3B. HCT was beneficial in patients with t-AML and AHD-AML alike, with an apparently stronger benefit in younger and male patients with adverse-risk cytogenetics.

Propensity Score Matching Analysis of HCT versus Chemotherapy Consolidation in s-AML

To further validate the comparison between HCT and conventional postremission therapy (CPRT) in patients with s-AML, a propensity score-matching analysis adjusting for major confounding factors was performed. Matching criteria were type of s-AML (AHD-AML or t-AML), cytogenetic risk group, age, and year of diagnosis. Patients with CR1 for <90 days were excluded. The model matched 45 patients undergoing HCT against 66 patients treated with CPRT (characteristics listed in Supplementary Table S2). The projected 5-year OS was significantly higher in the HCT group compared with the CPRT group (48% versus 20%; $P = .014$, log-rank test) (Figure 4A). In addition, 5-year relapse-free survival was superior in the HCT group compared with the CPRT group (43% versus 21%; $P = .021$, log-rank test) (Figure 4B).

Prognostic Factors for Outcome after HCT in s-AML

Among the patients with s-AML who underwent HCT, 34% developed acute GVHD (aGVHD) grade II or higher; 25% and 24% developed mild and moderate/severe chronic GVHD (cGVHD), respectively; and 51% did not develop cGVHD (Table 3). We analyzed prognostic factors predicting outcomes in the 100 patients with s-AML who underwent HCT in CR1 (Supplementary Figures S4 to S6 and Tables S2 and S3). Survival was favorably associated with peripheral stem cells rather than bone marrow as the graft source, mild cGVHD versus no cGVHD, and aGVHD of grade 0-I versus grade II-IV. There was no difference in survival associated with recipient age or sex, type of s-AML, cytogenetic risk, donor age, female donor to male recipient HCT, early or late transplantation period (1997 to 2004 versus 2005 to 2014), Hematopoietic Cell Transplantation-Specific Comorbidity Index score, myeloablative or nonmyeloablative conditioning, or cytomegalovirus reactivation. In a multivariable analysis, only the presence of mild cGVHD versus no cGVHD and the absence of acute GVHD grade >I were significantly associated with better survival (Supplementary Table S3). Note that due to a lack of dates for aGVHD and cGVHD, these variables could not be modeled as time-dependent covariates in the Cox models.

DISCUSSION

s-AML, including t-AML and AHD-AML, constitutes a significant proportion of all AML cases. Nonetheless, these subtypes of AML are often excluded from clinical trials and were previously not entered into the US Surveillance, Epidemiology, and

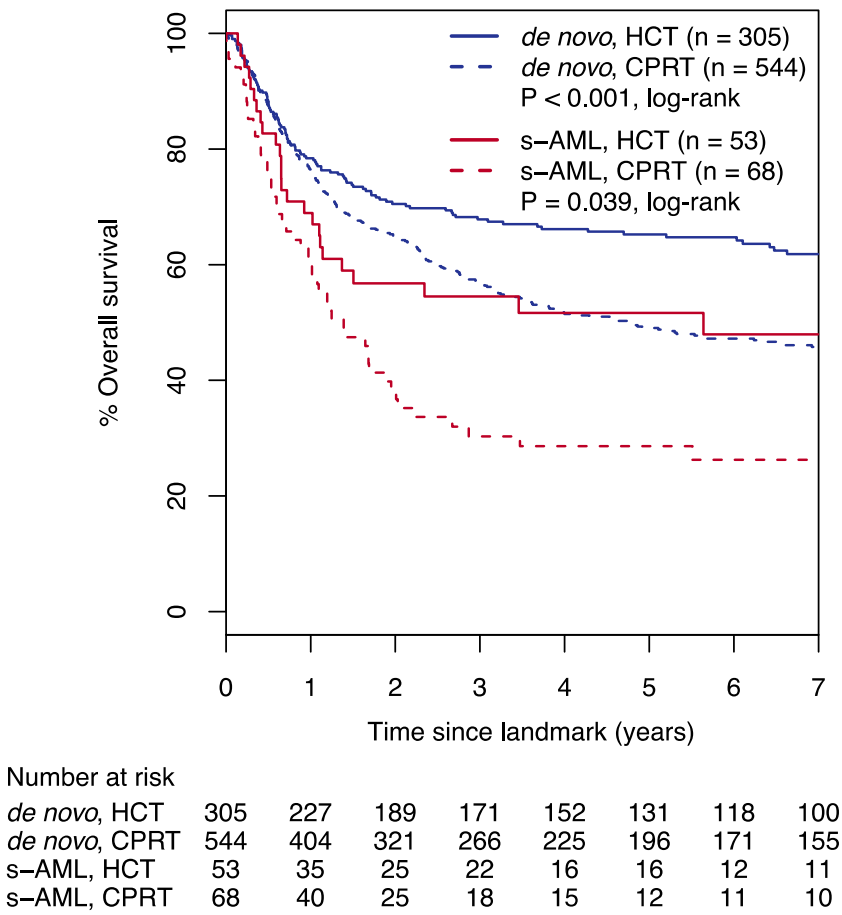

Figure 2. OS after landmark day 200, allogeneic HCT compared with CPRT in patients with de novo AML and patients with s-AML. Patients age >65 years and those with a favorable karyotype are excluded.

End Results (SEER) program. Consequently, s-AML has been much less widely studied than de novo AML. Although s-AML has been associated with poor outcomes, transplantation recommendations remain unclear, and s-AML is not included in the current ELN risk stratification [7]. In this study, we aimed to define the extent to which patients with s-AML undergo HCT and also to examine the role of HCT in treating s-AML in a large population-based cohort representing a real-life setting, including all Swedish patients diagnosed over a 17-year period.

The rates of HCT overall and at CR1 were relatively similar in the de novo AML and s-AML patient groups. In our study cohort, 23% of the patients (de novo AML, t-AML, and AHD-AML groups combined) underwent HCT in CR1. This proportion is slightly higher than the 19% reported in a Danish population-based registry over approximately the same time period [1]. In contrast, a British trial examining data from 1988 to 2009 found that 31% of the patients with AML who achieved CR underwent HCT [28]. However, that patient cohort was younger than ours and not population-based, and thus would be expected to show a higher rate of transplantation. This emphasizes the role of population-based studies for accurate real-world data on the rate of HCT in patients with AML.

Strikingly, there were virtually no long-term survivors among patients with s-AML who did not undergo HCT, and the vast majority of long-term survivors had undergone HCT, suggesting that HCT is the sole realistic curable treatment option for s-AML. Obviously, although crude survival figures for patients with and without HCT provide real-life data on outcomes in a population-based setting, they do not define the actual benefit of HCT. Therefore, we used several approaches to better define comparable groups, including a matched analysis similar to that used previously to evaluate the role of HCT in de novo AML [2]. These analyses showed persistently improved outcomes after HCT compared with CPRT in adjusted analyses, in both multivariable analysis and matching models. The survival benefit of HCT as postremission treatment in CR1 was significant in unfavorable-risk s-AML in a day 200 landmark analysis. In a multivariable analysis, HCT was identified as a significant positive survival parameter for s-AML. We also provided results for patients with de novo AML to examine the data for s-AML in the context of AML in the general population. Finally, in the matched analysis of patients with s-AML, both OS and relapse-free survival were significantly better in the patients who underwent HCT than in those who did not (5-year OS, 48% versus 20%).

Ideally, the role of transplantation in s-AML should be evaluated in a prospective randomized trial, minimizing the risk of any bias. However, such a trial is lacking and most likely will never be performed. Thus, a study such as this, based on large population-based retrospective cohort, is the best available tool for addressing the issue of HCT in s-AML. This approach has some limitations, however. Although a landmark analysis overcomes an inherent immortal time bias, achieving perfectly balanced groups is difficult, and an arbitrary landmark cutoff must be chosen. The propensity score-matched comparison

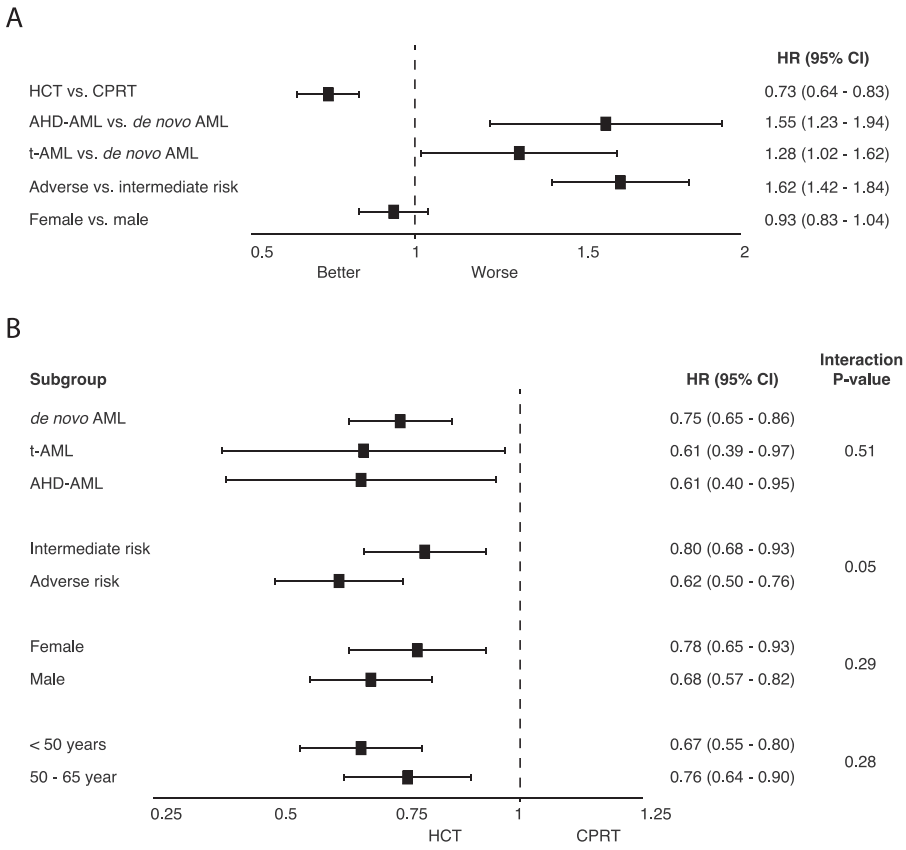

Figure 3. Survival hazards analysis and subgroup analysis. Patients age >65 years and those with a favorable karyotype are excluded. (A) Multivariable Cox regression analysis in de novo AML and s-AML combined. (B) Forest plot showing the impact of allogeneic HCT versus CPRT in subgroups of patients. HR, hazard ratio.

aimed to correct for selection bias; however, a disadvantage of this is that it reduces the number of patients available for comparison.

The only significant factors associated with better survival after HCT in the s-AML group were the presence of mild cGVHD and absence of severe aGVHD. However, it should be noted that owing to the absent debut date of GVHD, aGVHD and cGVHD could not be modeled as time-dependent covariates. Although patients who did not survive for >100 days were excluded from the analysis of cGVHD, the associations between GVHD and survival should be interpreted with caution, also due to the relatively low number of patients. Nonetheless, no patient- or AML-related factors, such as cytogenetics and age, were significant in univariable or multivariable analyses. An EBMT study including almost 5000 patients with s-AML identified active disease, adverse cytogenetics,

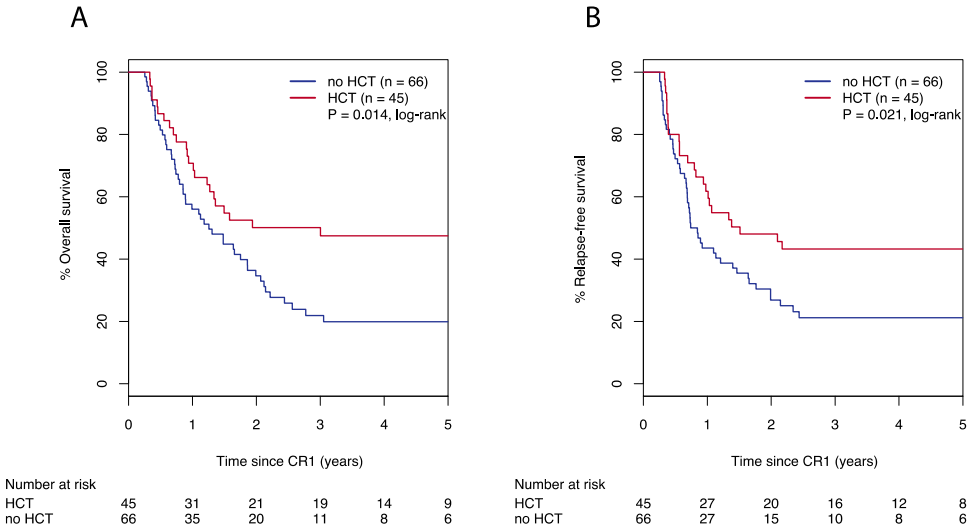

Figure 4. Matched analysis in patients with s-AML. OS (A) and relapse-free survival (B) in matched s-AML patients in CR1, comparing patients undergoing HCT and those receiving conventional postremission therapy (characteristics of matched patient groups listed in Supplementary Table S2).

older age, poor performance status, ex vivo T cell depletion, other malignant hematologic diseases, and patient cytomegalovirus seropositivity as associated with inferior OS in patients with s-AML who underwent HCT [10].

Lim et al [8] investigated the outcome after HCT in elderly patients with MDS, of which a large proportion (549 patients) had s-AML. Their key finding was that recipient age was a less significant factor than disease stage. Although this issue was not explored further in our present study, HCT appeared to be equally beneficial in patients age <50 years and those age >50 years. Litzow et al [9] identified age >35 years, poor-risk cytogenetics, refractory disease, and lack of a well-matched donor as risk factors for HCT in a study of 868 patients with t-AML and treatment-related MDS (t-MDS). However, their study cohort included pediatric patients, and the median patient age was only 40 years.

Other, smaller studies also have investigated the role of HCT in treating s-AML. Alam et al [29] identified use of an unrelated donor graft and adverse cytogenetics as significant risk factors for OS in a cohort of 65 patients with t-AML/t-MDS, but only 31 of these patients received induction treatment and achieved CR before undergoing HCT. Finke et al [30] followed 79 patients with t-AML after HCT, but only 19 of these patients had achieved CR1, complicating any comparison between their data and our present findings. Michelis et al [31] focused on the differences in outcomes between 180 patients with de novo AML and 84 patients with s-AML who underwent HCT in CR1 and, in contrast to our results, found no difference between the groups, perhaps owing to a smaller study series.

Taken together, the results of the comparative analyses in this study suggest that HCT is preferable to consolidation without HCT for achieving long-term survival. The outcomes without HCT were dismal in all types of s-AML, but especially for AHD-AML and particularly for MPN-AML. The poor outcomes were independent of the overrepresentation of poor-risk cytogenetics in patients with s-AML [32]. This suggests that s-AML has intrinsic properties not conveyed by cytogenetics, such as specific mutations that recur in AML or other patient-related factors that we were unable to analyze. Studies on the role of mutational data for HCT in s-AML are warranted. A recent study of MDS and s-AML suggested particularly poor outcomes in patients with *TP53* or *RAS* pathway mutations in combination with a complex karyotype or myelodysplastic/myeloproliferative neoplasms [33]. In addition, our study period was largely before the more recent era of expanded use of hypomethylating drugs, which have the potential to change the course of disease after transplantation. Moreover, the increasing use of minimal residual disease techniques and innovative pre-transplantation and post-transplantation treatments using both conventional and novel targeted drugs, also may change the course of the disease in the future, with or without transplantation.

In conclusion, our findings suggest that HCT is a realistic alternative curative treatment for s-AML and thus should be considered for all affected patients who are otherwise eligible and fit for transplantation. Further molecular characterization of s-AML is key to understanding the differences between outcomes in these groups and to aid the selection of treatment modality.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.05.038.

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