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Long-Term Outcomes After Autologous Versus Allogeneic Stem Cell Transplantation in Molecularly-Stratified Patients With Intermediate Cytogenetic Risk Acute Myeloid Leukemia: A PETHEMA Study

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A B S T R A C T

Acute myeloid leukemia (AML) with intermediate risk cytogenetics (IRcyto) comprises a variety of biological entities with distinct mutational landscapes that translate into differential risks of relapse and prognosis. Optimal postremission therapy choice in this heterogeneous patient population is currently unsettled. In the current study, we compared outcomes in IRcyto AML recipients of autologous (autoSCT) (n = 312) or allogeneic stem cell transplantation (alloSCT) (n = 279) in first complete remission (CR1). Molecular risk was defined based on *CEBPA, NPM1*, and *FLT3*-ITD mutational status, per European LeukemiaNet 2017 criteria. Five-year overall survival (OS) in patients with favorable molecular risk (FRmol) was 62% (95% confidence interval [CI], 50-72) after autoSCT and 66% (95% CI, 41-83) after matched sibling donor (MSD) alloSCT (P = .68). For patients of intermediate molecular risk (IRmol), MSD alloSCT was associated with lower cumulative incidence of relapse (P < .001), as well as with increased nonrelapse mortality (P = .01), as compared to autoSCT. The 5-year OS was 47% (95% CI, 34-58) after autoSCT and 70% (95% CI, 59-79) after MSD alloSCT (P = .02) in this patient subgroup. In a propensity-score matched IRmol subcohort (n = 106), MSD alloSCT was associated with superior leukemia-free survival (hazard ratio [HR] 0.33, P = .004) and increased OS in patients alive 1 year after transplantation (HR 0.20, P = .004). These results indicate that, within IRcyto AML in CR1, autoSCT may be a valid option for FRmol patients, whereas MSD alloSCT should be the preferred postremission strategy in IRmol patients.

INTRODUCTION

Postremission treatment intensification with an allogeneic stem cell transplantation (alloSCT) has been shown to reduce relapse risk and contribute to sustained disease remission and eventual cure in patients with acute myeloid leukemia (AML) [1,2]. Yet, despite its positive impact on relapse rates, the occurrence of severe transplant-related complications can offset the overall benefit of alloSCT [3,4]. As an alternative postremission strategy, consolidation with an autologous stem cell transplant (autoSCT) is associated with a more benign safety profile, which may be otherwise counterbalanced by an increased incidence of relapse in the absence of immune-mediated graft-versus-leukemia effect [5]. The optimization of this trade-off between antileukemic activity and treatment-related deleterious effects represents a challenge for postremission therapy selection, requiring an increasingly complex integration of multiple patient, transplant, and disease-specific variables that ultimately determine the individual risks of relapse versus treatment-related mortality [6,7]. Among these predictive variables, cytogenetic analysis has proved a useful tool for the identification of patient subgroups that might preferentially benefit (or not) from receiving an alloSCT after the achievement of a first complete remission (CR1) [8-12]. In this regard, there is a well-established consensus on the need for alloSCT intensification in patients with adverse risk cytogenetics (ARcyto), whereas patients with AML with core-binding factor translocations may be spared from alloSCT if an optimal response is obtained after frontline therapy [13-16]. However, postremission therapy choice is still a matter of debate for those patients assigned to the larger category of intermediate risk cytogenetics (IRcyto), since a number of studies in this setting have historically resulted in conflicting data [13-18]. IRcyto AML comprises a variety of biological entities with distinct mutational landscapes that translate into differential risks of relapse and prognosis [19-21]. Most notably, nucleophosmin-1 (*NPM1*) mutations and fms-like tyrosine kinase 3 internal tandem duplications (*FLT3*-ITD) constitute frequent molecular events whose interaction enables a further segregation of patients with favorable and adverse risk profiles within the IRcyto category [22,23]. To date, it remains nonetheless unsettled whether autoSCT is a valid alternative to alloSCT for patients in the molecular IR category (IRmol), particularly in the light of trends of decreasing treatment-related mortality after alloSCT and significant advances in the use of unrelated and alternative donor sources [24-28].

In the present study, we retrospectively analyzed transplant outcomes in a large cohort of IRcyto AML patients who received either an autoSCT or an alloSCT in CR1 after intensive chemotherapy within successive PETHEMA protocols since the year 2000. Cytogenetic stratification was refined with the incorporation of *NPM1* and *FLT3*-ITD mutational status, allowing for additional analyses on the impact of postremission therapy in a homogeneous propensity score (PS)–matched subcohort of IRmol patients.

METHODS

Data collection and study population

This is a registry-based retrospective analysis from the Programa Español de Tratamientos en Hematología (PETHEMA) Cooperative Study Group (NCT02607059). All patients provided written informed consent authorizing the use of their personal information for research purposes, and the study was approved by the institutional review boards of all the participating centers.

Inclusion criteria for the study were a diagnosis of nonpromyelocytic AML from 2000 onward, intermediate risk cytogenetics per Medical Research Council (MRC) criteria [12], achievement of a CR after no more than 2 induction chemotherapy cycles, and having received an autoSCT or an alloSCT in CR1.

Treatment

Frontline therapy within PETHEMA 99, 2007, and 2010 protocols consisted of 3 + 7 induction chemotherapy with idarubicin 12 mg/m^2 (days 1-3) and cytarabine 200 mg/m^2 (days 1-7). Consolidation was administered with the same induction scheme or high-dose cytarabine-based cycles. Less fit patients or those aged over 65 years included in the PETHEMA 99 and 2007 protocols received deintensified chemotherapy with idarubicin and cytarabine (2 + 5 schedule or reduced idarubicin and cytarabine dosing). Neither post-transplantation maintenance strategies nor the use of frontline FLT3 inhibitors was considered in the PETHEMA protocols evaluated in the study. In the PETHEMA 99 protocol, postremission choice of autoSCT versus alloSCT intensification in patients with IRcyto was solely based on the availability of an HLA-matched sibling donor (MSD), in whose absence autoSCT was the predefined option. In the PETHEMA 2007 and 2010 protocols, risk-adapted postremission therapy was planned for IRcyto patients: (1) alloSCT was recommended if a MSD was available except for patients with *NPM1*-mutated AML with *FLT3*-ITD wild-type (wt) or a *FLT3*-ITD with low allelic ratio (≤ 0.7) in whom an autoSCT was the preferred option, and (2) patients requiring two induction cycles to achieve CR1, and those with post-induction measurable residual disease (MRD) positivity (> 0.1%, local laboratory) or a high *FLT3*-ITD allelic ratio (> 0.7, local laboratory) were recommended to undergo an alloSCT from a MSD or from other donor types (non-MSD) if no MSD was available. Despite these guideline recommendations, the non-MSD alloSCT modality was performed off-protocol in some patients, per institutional criteria.

Endpoints and definitions

The study endpoints were overall survival (OS), cumulative incidence of relapse (CIR), leukemia-free survival (LFS), and non-relapse mortality (NRM).

OS was defined as the time to death from any cause. LFS was defined as the time to documentation of active disease or death. CIR was defined as the time to documentation of active disease, with death without evidence of relapse as a competing event. NRM was defined as time to death from any cause in the absence of prior documentation of active disease, with relapse being considered a competing event. All time-to-event outcomes in the primary analysis were computed from the date of transplantation. Patients with no event were censored at the date of their last follow-up.

Active disease was defined as the presence of ≥5% bone marrow blasts, detectable blasts in peripheral blood, or extramedullary disease. Cytogenetic risk stratification was made according to the MRC classification [12]. Molecular risk was defined based on *CEBPA, NPM1* and *FLT3*-ITD mutational status, per European LeukemiaNet (ELN) 2017 criteria [29], as follows: (1) favorable molecular risk (FRmol) if *CEBPA* biallelic mutation, or *NPM1*-mutated and *FLT3*-ITD-wt or with allelic ratio < 0.5; (2) IRmol if *NPM1*-mutated and *FLT3*-ITD with allelic ratio ≥ 0.5, or NPM1-wt and *FLT3*-ITD with allelic ratio < 0.5; and (3) adverse molecular risk (ARmol) if *NPM1*-wt and *FLT3*-ITD mutated with allelic ratio ≥ 0.5. Noncentralized MRD assessments were performed in a subset of patients by multiparameter flow cytometry, per institutional protocols. A threshold of 0.1% was established for postinduction MRD positivity. Noncentralized molecular profiling data was provided by each participating center.

Statistical analysis

The Wilcoxon rank-sum or the Kruskal-Wallis tests for continuous variables and the Pearson's chi-square or Fisher tests for categorical variables were used to compare patient, disease and treatment characteristics. Separate analyses were performed in different patient sets, as follows: (1) autoSCT versus MSD alloSCT in all IRcyto patients, in a mutation-agnostic manner; (2) autoSCT versus MSD alloSCT in molecularly-stratified IRcyto patients (FRmol and IRmol); (3) autoSCT versus MSD alloSCT in a subcohort of propensity score (PS)-matched IRmol patients; (4) non-MSD alloSCT recipients. Probabilities of OS and LFS were estimated using the Kaplan-Meier method. Cumulative incidences were used to estimate CIR and NRM in the setting of competing risks. Univariate analyses were performed using the log-rank test for OS and LFS, and the Gray's test for CIR and NRM. A multivariate logistic regression model for treatment allocation (autoSCT versus alloSCT) was constructed for the estimation of PS in IRmol patients. Age, sex, leukocyte count at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance score at diagnosis, number of cycles until achievement of CR, and treatment protocol were included as covariates in the model. Single nearest-neighbor PS matching without replacement was then performed. Subjects were matched on the logit of the PS using a caliper of width equal to 0.2 times the standard deviation of the logit of the PS [30]. Changes in standardized percentage bias, Rubin's R and Rubin's B were used to assess balance after PS matching. A pair-stratified univariate Cox proportional hazards model was fitted to evaluate the association between transplant type and survival outcomes in the matched cohort. All tests were 2-sided, and the type-1 error rate was fixed at 0.05. Statistical analyses were conducted in Stata 13 (StataCorp, College Station, TX) and R 3.5.3 (R Core Team 2019).

RESULTS

Patient, disease and treatment characteristics

Baseline characteristics are summarized in Table 1. A total of 591 patients fulfilled the inclusion criteria for the study. In total, 312 (53%) patients received an autoSCT, 183 (31%) were recipients of an MSD alloSCT, and 96 (16%) underwent a non-MSD alloSCT. As compared to patients in the MSD alloSCT group, those who received an autoSCT were more likely to harbor an *NPM1* mutation (59% versus 32%; $P < .001$) and to belong to the favorable ELN 2017 genetic risk category (57% versus 17%; $P < .001$), as well as less likely to harbor *FLT3*-ITD mutations with a high (≥0.5) allelic ratio (5% versus 22%; $P < .001$), to have a positive postinduction MRD determination (31% versus 49%; $P = .004$), and to have required two induction cycles for the achievement of CR1 (4% versus 9%; $P = .007$). Additionally, recipients of MSD alloSCT were slightly younger (median age of 48 versus 52 years; $P = .011$) and had lower ECOG scores than patients in the autoSCT group ($P = .031$). Patients in the non-MSD alloSCT cohort had an overall distribution of baseline characteristics more similar to MSD alloSCT recipients, although a higher proportion had positive postinduction MRD (71% versus 49%; $P < .001$) or had not achieved CR after 1 induction cycle (24% versus 9%; $P < .001$). Non-MSD alloSCT was a rarely selected option in the first half of the study time frame, becoming increasingly used in the more recent period (76% of non-MSD alloSCT were performed since 2011, and 45% between 2015 and 2019, the corresponding figures for the whole alloSCT cohort being 59% and 29%, respectively). This trend was paralleled by a shift toward a more favorable risk profile over time in the autoSCT cohort (46% of patients fell into the ELN 2017 favorable risk category between 2000 and 2009, and 61% for patients included since 2010 [$P = .02$]). Consolidation chemotherapy consisted of 2 cycles of treatment in a very large majority (93%) of autoSCT recipients, whereas 1 single consolidation course was administered in 64% of MSD and 61% of non-MSD recipients ($P < .001$), following protocol recommendations for additional consolidation chemotherapy in patients not undergoing alloSCT. Median time from diagnosis to transplantation was accordingly longer in the autoSCT group (182 days versus 133 and 165 days in the MSD alloSCT and non-MSD alloSCT groups, respectively). Median follow-up was shorter in non-MSD alloSCT recipients (21 months versus 56 and 47 months in the MSD alloSCT and autoSCT cohorts, respectively).

Outcomes of autoSCT versus MSD alloSCT in intermediate cytogenetic risk patients

A first analysis was carried out in all IRcyto patients in a mutation-agnostic manner. MSD alloSCT was associated with increased long-term OS and LFS as compared to autoSCT. The 2- and 5-year unadjusted estimates of OS were 79% (95% CI, 72-84) and 71% (95% CI, 63-77) in the MSD alloSCT group, as compared to 67% (95% CI, 61-72) and 54% (95% CI, 48-60) in the autoSCT group ($P = .002$) (Figure 1A). Similarly, 2- and 5-year unadjusted estimates of LFS were 72% (95% CI, 65-78) and 66% (95% CI, 58-73) in the MSD alloSCT cohort, and 54% (95% CI, 48-60) and 43% (95% CI, 37-49) in the autoSCT cohort ($P < .001$) (Figure 1B). Reduced-intensity conditioning (RIC) was associated with a decreased LFS ($P = .03$) but did not have a significant impact on OS ($P = .21$) as compared to myeloablative conditioning (MAC).

Recipients of an autoSCT had a higher CIR as compared to patients who underwent an MSD alloSCT. The 2- and 5-year CIR were 17% (95% CI, 12-23) and 20% (95% CI, 14-26) in the MSD alloSCT group, and 41% (95% CI, 35-47) and 50% (95% CI, 43-56) in the autoSCT group ($P < .001$) (Figure 1C). Conversely, NRM was lower in patients who underwent an autoSCT. The 2- and 5-year NRM rates were 11% (95% CI, 7-16) and 14% (95% CI, 9-20) in the MSD alloSCT group, and 5% (95% CI, 3-7) and 6% (95% CI, 4-10) in the autoSCT group ($P = .006$) (Figure 1D).

Outcomes of autoSCT versus MSD alloSCT in molecularly defined subgroups

Recipients of autoSCT and MSD alloSCT with available mutational data on *CEBPA, NPM1*, and *FLT3*-ITD status allowing for molecular risk stratification per ELN 2017 criteria were analyzed separately. Because very few patients were in the ARmol category based on *NPM1* and *FLT3*-ITD status (n = 15), outcomes could not be evaluated in this specific subgroup. Transplantation outcomes are shown in Table 2, and patient characteristics in the favorable (FRmol) and IRmol groups are shown in Supplementary Tables S1 and S2, respectively.

OS was similar among patients in the FRmol group after autoSCT (n = 115) versus MSD alloSCT (n = 24) ($P = .68$), as the increased CIR after autoSCT was counterbalanced by the risk of NRM after MSD alloSCT (Supplementary Figure S1 A-D). These trends were maintained in subanalyses considering differences in time to transplant between patients in the autoSCT and

Table 1
Patient, Disease, and Transplant Characteristics

	AutoSCT (n = 312)	MSD alloSCT (n = 183)	P*	Non-MSD alloSCT(n = 96)	P†
Median follow-up, months (IQR)	47.2 (16.0-91.7)	55.9 (19.9-109.0)	.17	20.5 (11.6-38.1)	<.001
Median age at diagnosis, years (IQR)	51.8 (40.2-58.9)	47.8 (38.1-56.0)	.011	50.7 (39.6-55.7)	.026
Female sex, n (%)	168 (53.8)	94 (51.4)	.59	54 (56.3)	.73
ECOG, n (%)			.031		.10
0	101 (39.1)	81 (51.6)		32 (40.5)	
1	115 (44.6)	60 (38.2)		33 (41.8)	
2	42 (16.3)	16 (10.2)		14 (17.7)	
Missing	54	26		17	
Median WBC count at diagnosis, x$10^3/\mu$L (IQR)	13.4 (4.0-46.9)	9.0 (2.4-48.9)	.11	11.7 (3.0-59.0)	.26
Median BM blasts at diagnosis, % (IQR)	42.5 (12.0-75.5)	30.0 (6.0-78.0)	.13	60.0 (20.0-84.9)	.022
AML subtype, n (%)			.008		.031
Secondary	14 (4.7)	20 (11.1)		8 (8.6)	
Missing	15	3		3	
Cytogenetics			.06		.06
Normal karyotype	254 (81.4)	136 (74.3)		69 (71.9)	
Abnormal karyotype (intermediate MRC risk)	58 (18.6)	47 (25.7)		27 (28.1)	
NPM1 status, n (%)			<.001		<.001
Negative	88 (41.1)	99 (68.3)		51 (62.2)	
Positive	126 (58.9)	46 (31.7)		31 (37.8)	
Missing	98	38		14	
FLT3-ITD status, n (%)			<.001		<.001
Negative	194 (85.8)	108 (72.5)		52 (62.7)	
Positive (ratio <0.5)	12 (5.3)	4 (2.7)		9 (10.8)	
Positive (ratio ≥0.5)	12 (5.3)	32 (21.5)		19 (22.9)	
Positive (unknown ratio)	8 (3.5)	5 (3.4)		3 (3.6)	
Missing	86	34		13	
CEPBA biallelic mutation status, n (%)			.75		.92
Negative	69 (97.2)	51 (98.1)		29 (96.7)	
Positive	2 (2.8)	1 (1.9)		1 (3.3)	
Missing	241	131		66	
ELN 2017 risk stratification, n (%)			<.001		<.001
Favorable	115 (56.7)	24 (17.4)		14 (18.2)	
Intermediate	85 (41.9)	102 (73.9)		60 (77.9)	
Adverse	3 (1.5)	12 (8.7)		3 (3.9)	
Missing	109	45		19	
PETHEMA protocol, n (%)			.12		<0.001
99	117 (37.5)	50 (27.3)		10 (10.4)	
2007	75 (24.0)	49 (26.8)		20 (20.8)	
2010	120 (38.5)	84 (45.9)		66 (68.8)	
Cycles to achieve CR, n (%)			.007		<.001
1	301 (96.5)	166 (90.7)		73 (76.0)	
2	11 (3.5)	17 (9.3)		23 (24.0)	
Post-induction MRD status, n (%)			.004		<.001
Negative	118 (68.6)	52 (51.0)		18 (29.5)	
Positive	54 (31.4)	50 (49.0)		43 (70.5)	
Missing	140	81		35	
Median time to transplant, days (IQR)	181.5 (156.5-214.0)	133.0 (115.0-161.0)	<.001	164.5 (130.5-197.5)	<.001
Conditioning intensity, n (%)					.70
Myeloablative		115 (73.7)		51 (70.8)	
Reduced intensity		39 (25)		19 (26.4)	
Non-myeloablative		2 (1.3)		2 (2.8)	
Missing		27		24	
Conditioning regimen, n (%)					
FluBu	—	64 (43.5)		6 (8.5)	
TBF	—	—		25 (35.2)	
BEA	218 (81.3)	—		—	
BuCy	44 (16.4)	31 (21.1)		7 (9.9)	

(*continued*)

Table 1 (*Continued*)

	AutoSCT (n = 312)	MSD alloSCT (n = 183)	P*	Non-MSD alloSCT(n = 96)	P†
Other	6 (2.2)	52 (35.4)		33 (46.5)	
Missing	44	36		25	
Non-MSD donor type, n (%)					
MUD				30 (31.3)	
MMUD				27 (28.1)	
Mismatched related				7 (7.3)	
Haploidentical				32 (33.3)	
Post-remission consolidation cycles, n (%)			<.001		<.001
1 cycle	6 (3.4)	54 (64.3)		17 (60.7)	
2 cycles	165 (93.2)	26 (31.0)		7 (25.0)	
3 cycles	6 (3.4)	4 (4.8)		4 (14.3)	
Missing	135	99		68	

IQR indicates interquartile range; WBC, white blood cell; BM, bone marrow; FluBu, fludarabine/busulfan; TBF, thiotepa/busulfan/fludarabine; BEA, busulfan/etoposide/cytarabine; BuCy, busulfan/cyclophosphamide; MUD, matched unrelated donor; MMUD, mismatched unrelated donor.

* AutoSCT versus MSD alloSCT comparison.

† AutoSCT versus MSD alloSCT versus non-MSD alloSCT comparison.

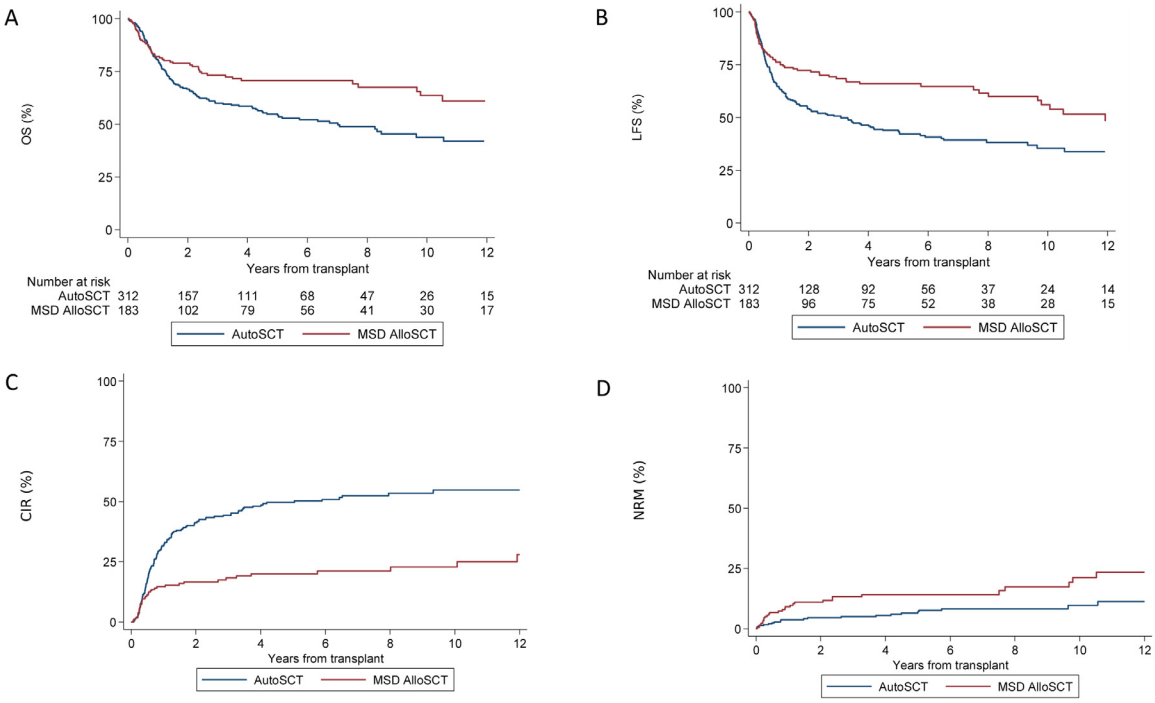

Figure 1. Outcomes after autoSCT or MSD alloSCT in patients with intermediate risk cytogenetics. (A) OS. (B) LFS. (C) CIR. (D) NRM.

alloSCT groups (data not shown). When focusing on patients in the IRmol category (n = 187), MSD alloSCT was associated with long-term benefits with respect to CIR (P< .001), LFS (P < .001), and OS (P= .02), as well as with increased NRM (P = .01), as compared to autoSCT (Figure 2 A-D). The majority of relapse events in the IRmol group occurred within the first year after

Table 2
Outcomes After AutoSCT or MSD AlloSCT in Patients of Favorable and Intermediate Molecular Risk

	AutoSCT					AlloSCT				
	n	OS	LFS	CIR	NRM	n	OS	LFS	CIR	NRM
2-year transplant outcomes										
Favorable risk	115	70 (59-79)	61 (50-70)	37 (27-46)	3 (0.7-7)	24	78 (55-90)	71 (48-85)	25 (10-44)	4 (0.3-18)
Intermediate risk	85	62 (50-71)	42 (31-53)	53 (41-63)	5 (2-11)	102	77 (67-85)	73 (63-81)	12 (6-19)	15 (9-23)
5-year transplant outcomes										
Favorable risk	115	62 (50-72)	52 (40-62)	45 (34-56)	3 (0.7-7)	24	66 (41-83)	59 (35-77)	25 (10-44)	16 (4-36)
Intermediate risk	85	47 (34-58)	33 (22-44)	59 (46-69)	7 (2-14)	102	70 (59-79)	67 (55-76)	15 (8-24)	18 (11-27)

95% CIs are shown in parentheses.

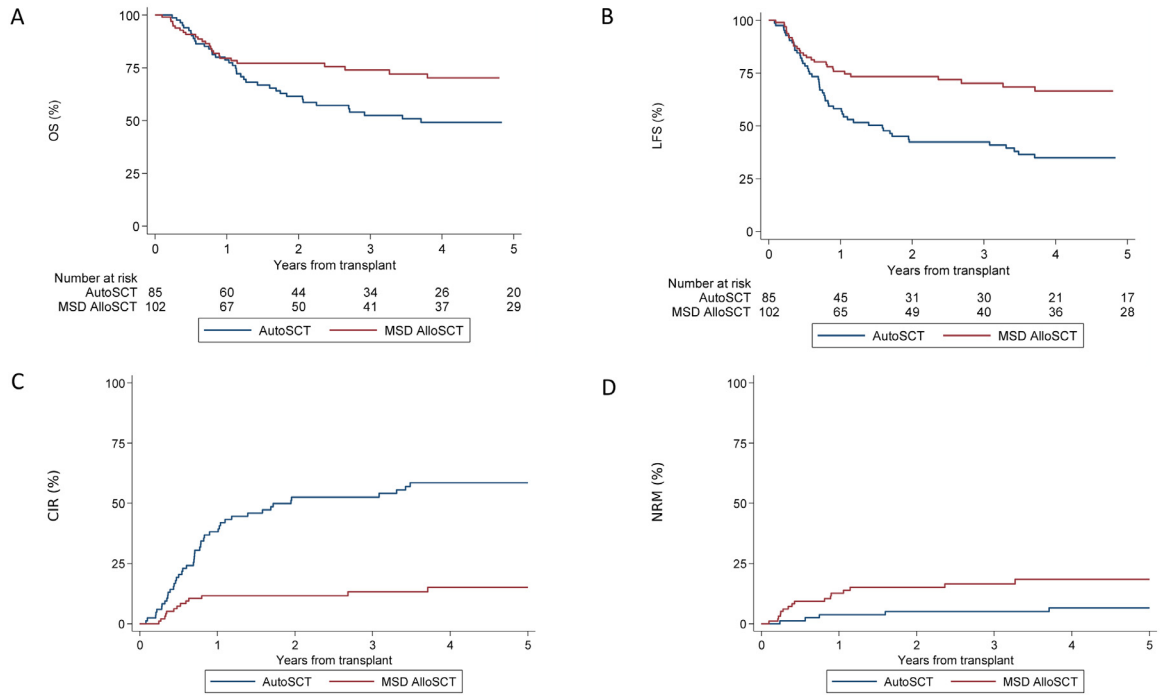

Figure 2. Outcomes after autoSCT or MSD alloSCT in patients with intermediate molecular risk (ELN 2017). (A) OS. (B) LFS. (C) CIR. (D) NRM.

MSD alloSCT (79%) or autoSCT (63%). Median and 2-year OS estimates after relapse were 6 months and 17% after autoSCT, and 4 months and 15% after alloSCT. In the subanalysis of IRmol patients who maintained a CR at 2 years from transplantation (n = 80), autoSCT remained associated with a higher long-term CIR (3-year CIR 14% versus 5%, *P*= .03). One (85% versus 72%) and 2-year (73% versus 63%) estimates of OS were longer in IRmol patients with available MRD status who achieved postinduction MRD negativity (n = 75/120), but these differences did not reach statistical significance (*P*= .23). Among MSD alloSCT recipients in the IRmol group, there was no association between conditioning intensity (n [MAC] = 61, n [RIC] = 27) and OS (*P*= .44) or LFS (*P*= .57). Additional subanalyses in the IRmol cohort were performed in different time periods (transplant before and after 2010), as well as considering time to transplantation and outcomes from the date of diagnosis. The aforementioned trends with respect to the impact of transplant type were preserved in these sensitivity analyses (data not shown).

Outcomes of autoSCT versus MSD alloSCT in IRmol patients: PS-matched analysis

A PS-matched analysis was performed in the IRmol subgroup. The distribution of baseline characteristics in the unmatched and matched cohorts is shown in Table 3. PS-matching resulted in an adequate balance for matched baseline variables (mean bias reduction = 64.1%, Rubin's B = 25.5, Rubin's R = 0.85). In the matched subcohort (n = 106), the 2- and 5-year estimates of OS were 84% (95% CI, 70-92) and 78% (95% CI, 62-88) in the MSD alloSCT group, and 64% (95% CI, 49-76) and 47% (95% CI, 31-60) in the autoSCT group (Figure 3 A). The 2- and 5-year LFS probabilities were 84% (95% CI, 70-92) and 75% (95% CI, 59-86) in the MSD alloSCT group, and 39% (95% CI, 26-52) and 32% (95% CI, 19-45) in the autoSCT group (Figure 3 B). In the pair-stratified Cox model, MSD alloSCT was associated with increased LFS (hazard ratio [HR] 0.33; 95% CI, 0.16-0.71; *P* = .004). Because of the early crossing of the OS curves, implying a departure from the proportional hazards assumption, separate exploratory analyses were carried out before and after 1 year of follow-up. There were no differences in OS during the first year after transplantation between either transplant type (stratified HR 0.70; 95% CI, 0.27-1.84; *P*= .47), whereas MSD alloSCT was associated with increased OS among those patients alive 1 year after transplantation (unstratified HR 0.20; 95% CI, 0.07-0.61; *P*= .004).

Transplant outcomes in non-MSD alloSCT recipients

When considering transplant outcomes in non-MSD alloSCT recipients with IR cytogenetics (n = 96) (Supplementary Figure S2 A-D), OS was inferior to that observed after autoSCT (*P* = .02) or MSD alloSCT (*P* < .001). On the other hand, LFS was comparable to that observed in autoSCT recipients (*P* = .21), but inferior with respect to the MSD alloSCT group (*P* < .001). CIR in non-MSD recipients was intermediate (*P*< .001), and NRM was higher (*P*< .001), as compared to autoSCT and MSD AlloSCT. These relative trends in transplant outcomes were also maintained in the subset of non-MSD alloSCT recipients belonging to the IRmol group (n = 60) (Supplementary Figure S3 A-D).

DISCUSSION

This long-term follow-up study shows that MSD availability and molecular risk may inform transplantation modality choice for IRcyto AML patients in CR1. Patients with IRmol AML who received an alloSCT from a MSD had improved survival as compared to those receiving an autoSCT, whereas autoSCT offered similar outcomes as compared to MSD alloSCT in FRmol patients.

Table 3
Patient and Disease Characteristics in the Unmatched and Propensity Score-Matched Intermediate Molecular Risk Cohorts

	Pre-matching cohort				Post-matching cohort				
	AutoSCT (n = 85)	MSD alloSCT (n = 102)	*P*	Standardized Bias (%)	AutoSCT (n = 53)	MSD alloSCT (n = 53)	*P*	Standardized Bias (%)	Bias Reduction (%)
Median follow-up, months (IQR)	52.1 (24.2-71.3)	34.4 (13.9-73.2)	.39	−8.1	47.2 (24.8-71.1)	54.2 (21.1-74.3)	.95	11.6	−43.5
Median age at diagnosis, years (IQR)	54.0 (44.2-58.5)	52.0 (42.0-57.9)	.28	−6.2	54.6 (41.5-59.9)	48.7 (40.9-57.8)	.22	-15.0	−141.7
Female sex, n (%)	47 (55.3)	46 (45.1)	.16	−25.8	26 (49.1)	30 (56.6)	.44	15.1	41.4
ECOG, n (%)			.11	−32.3			.95	5.4	83.3
0	29 (42.6)	50 (58.1)			27 (50.9)	26 (49.1)			
1	27 (39.7)	28 (32.6)			20 (37.7)	20 (37.7)			
2	12 (17.6)	8 (9.3)			6 (11.3)	7 (13.2)			
Missing	17	16			0	0			
Median WBC count at diagnosis, x10e3/μL (IQR)	5.5 (2.2-36.2)	6.8 (2.1-23.7)	.80	7.3	4.3 (2.2-23.2)	5.0 (1.5-23.4)	.45	−1.9	73.8
Median BM blasts at diagnosis, % (IQR)	39.0 (5.0-80.0)	27.0 (4.0-60.0)	.32	−25.7	38.0 (3.0-80.0)	30.0 (4.0-76.0)	.77	−11.0	57.1
Molecular subgroup (ELN 2017), n (%)			.027	30.7			.080	34.7	−12.9
*NPM1*neg/*FLT3*-ITDneg	73 (85.9)	82 (80.4)			47 (88.7)	42 (79.2)			
*NPM1*neg/*FLT3*-ITDpos (ratio < 0.5)	5 (5.9)	1 (1.0)			3 (5.7)	1 (1.9)			
*NPM1*pos/*FLT3*-ITDpos (ratio >= 0.5)	7 (8.2)	19 (18.6)			3 (5.7)	10 (18.9)			
Protocol, n (%)			.085	28.8			.98	0.0	100.0
99	13 (15.3)	11 (10.8)			7 (13.2)	7 (13.2)			
2007	35 (41.2)	30 (29.4)			16 (30.2)	15 (28.3)			
2010	37 (43.5)	61 (59.8)			30 (56.6)	31 (58.5)			
Cycles to achieve CR, n (%)			.27	23.2			.56	−7.2	69.1
1	81 (95.3)	93 (91.2)			51 (96.2)	52 (98.1)			
2	4 (4.7)	9 (8.8)			2 (3.8)	1 (1.9)			
Post-induction MRD status, n (%)			.016	40.1			.83	−4.6	88.6
Negative	42 (73.7)	33 (52.4)			26 (74.3)	26 (76.5)			
Positive	15 (26.3)	30 (47.6)			9 (25.7)	8 (23.5)			
Missing	28	39			18	19			
Median time to transplant, days (IQR)	182.0 (161.0-207.0)	130.5 (117.0-152.0)	<.001	−93.6	186.0 (162.0-206.0)	130.0 (117.0-143.0)	<.001	−104.9	−12.1

For the computation of propensity scores, age, sex, ECOG at diagnosis, WBC count at diagnosis, PETHEMA protocol and the number of induction cycles to achieve CR were included as covariates in the multivariate logistic regression model.

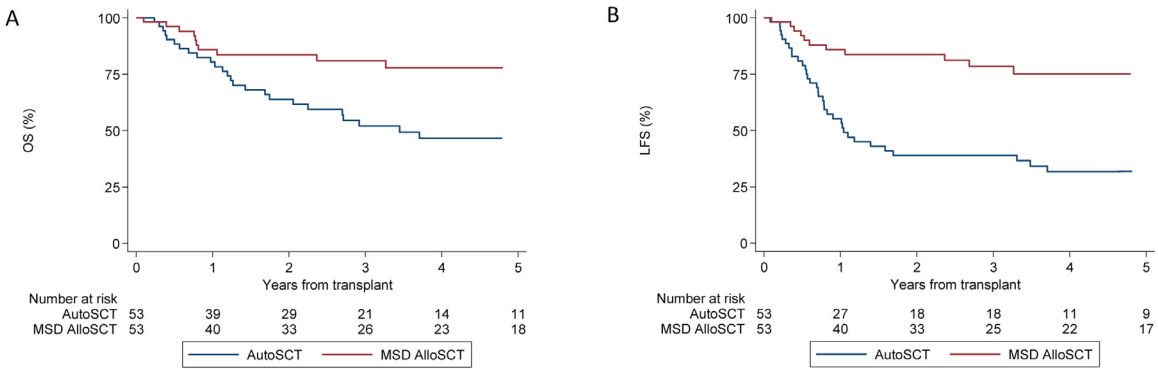

Figure 3. Outcomes after autoSCT or MSD alloSCT in PS-matched patients with intermediate molecular risk (ELN 2017). (A) OS. (B) LFS.

Results from a number of prospective clinical trials and meta-analyses support the use of alloSCT in intermediate and high-risk AML patients [14–16,18]. Nevertheless, although the latter is widely accepted, the indication of alloSCT for IRcyto AML within first-line treatment is still a matter of debate. This lack of consensus is reflected in the disparities in prevailing international expert group recommendations [29,31,32]. For many years, evidence in this scenario has relied on donor versus no-donor studies harnessing genetic randomization as a means to avoid selection bias in the allocation to postremission therapy and possibly leading to an underestimation of the benefit derived from alloSCT. Alternative approaches to the comparison of outcomes between post-remission therapies have emerged in more recent times, including landmark analyses or the inclusion of alloSCT as a time-dependent variable in regression models. In the present study, standard survival analysis could be used, since we compared time to event from transplantation in cohorts of patients in which the risk for immortal time bias was mitigated by the need to have reached the transplant itself.

In our initial mutation-agnostic analysis in IRcyto patients, MSD alloSCT was associated with superior outcomes as compared to autoSCT, with long-term improvements in LFS and OS. While the observed NRM rates in our series were kept within the expected range from other contemporary cohorts [33,34], the high risk of relapse after autoSCT was not compensated by its low morbidity. Overall, these results are consistent with data previously reported in a meta-analysis of prospective clinical trials where allocation to alloSCT was based on MSD availability, and outcomes were evaluated in an intention-to-treat analysis [16]. More recently, different studies have unveiled the diversity of mutational landscapes in IRcyto AML, adding additional layers of complexity to its prognostication [19-23]. In this context, we focused our analyses on the patient subsample with available *CEBPA, NPM1* and *FLT3*-ITD mutational status. A formal comparison between postremission therapy arms could not be performed in the subgroup of patients with *FLT3*-ITD mutations with a high ($\geq$ 0.5) allelic ratio and *NPM1*-wt because of the few numbers of patients falling into this category. In line with other reports [19,35,36], MSD alloSCT did not confer an advantage over autoSCT in patients with *NPM1*-mutated AML with *FLT3*-ITD-wt status or harboring *FLT3*-ITD mutations with a low allelic ratio ($<$0.5). In contrast, outcomes in the larger IRmol subgroup differed by type of postremission therapy, with benefits in 5-year LFS and OS rates of 34% and 23%, respectively, in the unmatched MSD alloSCT cohort with respect to autoSCT. These differences were apparent despite the more favorable baseline risk profile of patients undergoing an autoSCT. Likewise, these trends were preserved in the PS-matched subcohort. Of note, most patients were included in this IRmol category on the basis of both *NPM1*-wt and *FLT3*-ITD-wt status. This hindered our ability to separately investigate the role of postremission strategies in patients with *FLT3*-ITD mutations falling into the IRmol group per ELN 2017 criteria, in whom the use of autoSCT is particularly controversial [37]. Mutations in *TP53, RUNX1* or *ASXL1* are known to confer an adverse impact on outcomes, with the latter two clustering in the IRcyto group [21,38,39]. Unfortunately, given the retrospective design of our study, mutations in these genes were not analyzed. It appears nonetheless unlikely that molecular risk refinement per ELN 2017 criteria could have a substantial influence on our results given the low frequency of these 3 mutational events in the younger IRcyto AML population.

Interestingly, differential patterns in relapse kinetics were observed after autoSCT and MSD alloSCT, with the former characterized by a significantly higher risk of late relapse after 1 year after transplantation. Although several studies have described epigenetic immune evasion mechanisms underlying relapse after alloSCT [40,41], research is warranted on the clonal dynamics of post-autoSCT relapses, and its implications for appropriate patient selection, disease monitoring, and preemptive intervention. In additional post hoc subanalyses, MSD alloSCT was associated with a clinical benefit in IRmol AML irrespective of conditioning intensity. Although of exploratory nature, our results failed to replicate those reported by a Hemato-Oncologie voor Volwassenen Nederland (HOVON) group study showing an advantage for RIC versus MAC alloSCT or autoSCT [42]. In this regard, recently published data indicate that optimal conditioning intensity may depend on MRD status at the time of transplantation, considered neither in the HOVON nor the present study, with MAC resulting in improved OS only in patients with genomic evidence of MRD [43].

As expected, patients and disease characteristics differed between transplant modality groups. Since 2007, PETHEMA guidelines recommended to perform an autoSCT in the majority of FRmol patients, whereas for IRmol subjects the alloSCT versus autoSCT indication relied on the number of cycles to achieve CR, post-induction MRD, and MSD availability. However, other factors may have influenced patient and physician's decision regarding transplant type selection. In order to account for differences in IRmol AML patients, PS matching was additionally performed, allowing for the comparison of largely homogeneous patient groups in our primary analysis of MSD alloSCT versus autoSCT. On the other hand, non-MSD alloSCT was associated with a more adverse risk profile and increased CIR, suggesting that selection of this transplant modality was reserved for patients with high-risk features in

whom a suitable MSD was not available and autoSCT was deemed inappropriate.

Our study has intrinsic limitations as a result of its registry-based design and the rapidly evolving nature of AML research in recent years. Notably, a formal comparison of non-MSD alloSCT versus MSD alloSCT or autoSCT outcomes was precluded by the smaller sample size of this subgroup and a significant risk for unmeasured confounding. Also, the MRD-stratified impact of postremission therapy could not be analyzed in our series, because pretransplantation MRD status was not available. As with molecular profiling at diagnosis, MRD monitoring through either multiparameter flow cytometry or molecular techniques is being consolidated as a powerful tool for the prediction of transplant outcomes in AML and may be of help to guide transplant modality selection. In this respect, data from the GIMEMA AML1310 Study has supported a role for autoSCT in FLT3-ITD-wt IRmol patients who achieve MRD negativity after consolidation chemotherapy [44]. Last, novel strategies not considered in the hereby analyzed PETHEMA protocols have been consolidated as standard of care or have shown promising results in late-stage trials in recent years, such as the use of *FLT3* inhibitors as frontline or maintenance therapy, or treatment with oral azacytidine (CC-486) as maintenance in the non-alloSCT setting [45-47]. Future studies will be therefore required to reassess the comparative role of post-remission therapies in this evolving therapeutic landscape.

In conclusion, our long-term follow-up analyses in IRcyto AML in CR1 indicate that autoSCT is a valid option for FRmol patients, whereas MSD alloSCT should be the preferred postremission strategy in patients with IRmol AML. AutoSCT and non-MSD alloSCT may be alternatively used in IRmol patients without an available MSD. Further studies integrating MRD status and risk of NRM are needed to refine the relative positioning of transplant modalities on an individual basis.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2020.12.029.

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