Transplantation and Cellular Therapy 28 (2022) 773.e1–773.e8

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Haploidentical

Impact of Cytogenetic Risk on Outcomes of Non-T-Cell–Depleted Haploidentical Hematopoietic Cell Transplantation in Patients with Relapsed or Refractory Acute Myeloid Leukemia

Arnon Nagler[1], Myriam Labopin[2,3], Bhagirathbhai Dholaria[4,*], Fabio Ciceri[5], Alessia Fraccaroli[6], Didier Blaise[7], Renato Fanin[8], Benedetto Bruno[9], Edouard Forcade[10], Jan Vydra[11], Patrice Chevallier[12], Claude Eric Bulabois[13], Pavel Jindra[14], Martin Bornhäuser[15], Jonathan Canaani[16], Jaime Sanz[17], Bipin N. Savani[4], Alexandros Spyridonidis[18], Sebastian Giebel[19], Eolia Brissot[2], Ali Bazarbachi[20], Jordi Esteve[21], Mohamad Mohty[2,3]

[1] *Division of Hematology, Sheba Medical Center, Tel Hashomer, Israel*
[2] *Sorbonne University, Sevice d'hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, Paris, France*
[3] *ALWP of the EBMT Paris office, Paris, France*
[4] *Vanderbilt University Medical Center, Nashville, Tennessee*
[5] *IRCCS San Raffaele Hospital, University Vita-Salute, Milano, Italy*
[6] *Hematopoietic Stem Cell Transplantation, Department of Internal Medicine III, University Hospital, Munich, Germany*
[7] *Programme de Transplantation & Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France*
[8] *Azienda Ospedaliero Universitaria di Udine, Division of Hematology, Udine, Italy*
[9] *S.S.C.V. D Trapianto di Cellule Staminali A.O.U Citta della Salute e della Scienza di Torino, Torino, Italy*
[10] *CHU Bordeaux, Hôpital Haut-Leveque, Pessac, France*
[11] *Institute of Hematology and Blood Transfusion, Prague, Czech Republic*
[12] *CHU Nantes, Dept. D`Hematologie, Nantes, France*
[13] *CHU Grenoble Alpes - Université Grenoble Alpes, Service d`Hématologie, Grenoble, France*
[14] *Charles University Hospital, Dept. of Hematology/Oncology, Pilsen, Czech Republic*
[15] *Universitaetsklinikum Dresden Medizinische Klinik und Poliklinik I, Dresden, Germany*
[16] *Sheba Medical Center, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[17] *Hospital La Fe, Valencia, Spain*
[18] *Hematology Stem Cell Transplant Unit, School of Medicine, University of Patras, Patras, Greece*
[19] *Department of Bone Marrow Transplantation and Hematology-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[20] *Bone Marrow Transplantation Program, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon*
[21] *Hematology Department, Hospital Clinic, Barcelona, Spain*

Article history:
Received 30 May 2022
Accepted 15 August 2022

Key Words:
Allogeneic stem cell transplantation
Acute myeloid leukemia
Haploidentical
Cytogenetic risk
Relapse
Post-transplant cyclophosphamide

A B S T R A C T

Baseline cytogenetics and disease status are key factors predicting the outcomes of allogeneic hematopoietic cell transplantation (HCT) in patients with acute myeloid leukemia (AML). The importance of cytogenetic risk in patients with primary refractory or relapsed (R/R) AML undergoing haploidentical (Haplo) HCT is unknown. We studied the impact of cytogenetic risk in patients with R/R de novo AML with active disease who underwent non-T-cell–depleted Haplo-HCT with post-transplantation cyclophosphamide from 2010 to 2020. Four hundred forty patients with active disease at transplantation from the European Society for Blood and Marrow Transplantation database were analyzed (291 [66.1%] with intermediate-risk [AMLint] and 149 [44.1%] with adverse-risk cytogenetics [AMLadv]). Impact of baseline cytogenetic risk on various transplantation outcomes was evaluated. Pre-transplantation disease status was relapse in 48.1% and 26.8% and primary refractory in 51.9% and 73.2% of the patients with AMLint and AMLadv, respectively ($P < .0001$). Two-year leukemia-free survival (LFS, 35.5% versus 15.5%, $P = .001$) and overall survival (OS, 39.2% versus 20.1%, $P = .001$) were better in AMLint versus AMLadv. In multivariate analysis, the relapse rate was significantly higher (hazard ratio [HR] = 2.17 [95% confidence interval

Financial disclosure: See Acknowledgments on page 773.e7
A.N. and B.D. contributed equally and share authorship.
*Correspondence and reprint requests: Bhagirathbhai Dholaria, M.D., Department of Hematology-Oncology, 2220 Pierce Ave, 686 Preston Research Building, Vanderbilt University Medical Center, Nashville, TN 37232.
E-mail address: Bhagirathbhai.r.dholaria@vumc.org (B. Dholaria).

https://doi.org/10.1016/j.jtct.2022.08.018

{CI} 1.57-3.0]) and LFS (HR = 1.71 [95% CI, 1.31-2.22]) and OS (HR = 1.69 [95% CI, 1.29-2.22]), significantly lower for patients with AMLadv compared to AMLint, conditioning intensity did not affect leukemia relapse rate. Non-relapse mortality (HR = 1.1 [95% CI, 0.7-1.74]) and graft-versus-host disease–free, relapse-free survival (HR = 1.37 [95% CI, 1.06-1.77]) did not differ significantly between the risk groups. Disease status before transplant (primary refractory versus relapsed) or conditioning intensity did not impact main transplant outcomes. Baseline cytogenetic risk remains a key prognostic factor for patients with R/R AML with persistent disease before non-T-cell–depleted Haplo-HCT.

Acute myeloid leukemia (AML) is a devastating malignancy with a long-term survival of less than 20% [1,2]. The first goal in the therapeutic paradigm in AML and a prerequisite to long-term disease control is achievement of complete remission (CR) with induction chemotherapy [1,3]. However, up to 30% of AML patients fail to achieve CR and up to 50% will eventually relapse [4]. Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the standard postremission therapy for eligible patients with intermediate- and adverse-risk AML [1]. The use of HCT from a related haploidentical donor (Haplo-HCT) for patients with high-risk AML has been increasing in recent years [5,6]. Disease status at transplantation is one of the most important prognostic factors for HCT outcome, including Haplo-HCT [7] (Figure 1). Results of Haplo-HCT are better in first complete remission (CR1), and worsen in more advanced disease phases, especially for patients with active disease before transplantation [5,7]. Nonetheless, patients with R/R AML can still benefit from HCT, with a long-term overall survival (OS) between 25% to 30% [8–11]. A second critical prognostic factor for outcome in AML is underlying cytogenetics, predictive of both initial response and relapse risk after HCT [1,12-16]. Recently we addressed the prognostic role of the complete gamut of cytogenetic aberrations in 8558 adult AML patients who underwent HCT from either a matched sibling or a matched unrelated donor. Patients with inv(3) (q21q26)/t(3;3)(q21;q26), del(5q), monosomy 7, chromosome 17p abnormalities, t(10;11)(p11-14;q13-23), t(6;11)(q27;q23), as well as those patients with a monosomal or complex karyotype experienced significantly inferior leukemia-free survival (LFS) compared to patients with a normal karyotype [16]. The prognostic role of cytogenetic risk on transplantation outcome in AML patients with active leukemia at time of transplantation is less established. The impact of cytogenetic risk, stratified according to the United Kingdom Medical Research Council (UK-MRC) classification system was recently assessed in 2089 patients with R/R AML who underwent HCT from either sibling or unrelated donors, mostly HLA matched [17]. Intermediate- and adverse-risk cytogenetics were associated with higher incidence of relapse, translating into worse LFS and OS compared to the favorable-risk group [17]. However, the impact of cytogenetic risk on outcome of patients with R/R AML undergoing Haplo-HCT is unknown. Here, we aimed to investigate the impact of cytogenetic risk in patients with active AML undergoing Haplo-HCT.

PATIENTS AND METHODS

Study Design and Data Collection

This was a retrospective, multicenter analysis using the dataset of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a voluntary working group of more than 600 transplantation centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. EBMT minimum essential data forms are submitted to the registry by transplantation center personnel after written informed consent is received from patients in accordance with center ethical research guidelines. Accuracy of data is assured by the individual transplantation centers and by quality control measures such as regular internal and external audits. The results of disease assessments at HCT were also submitted and form the basis of this report. Eligibility criteria for this analysis included adult patients (≥18 years) with de novo AML with active disease defined as primary refractory, first or second relapse with >5% of residual morphologic blasts, with available intermediate or high-risk cytogenetics as defined by the UK-MRC and listed in Supplementary Table S1. Patients who received a first non-T-cell–depleted HCT with post-transplantation cyclophosphamide (PTCy) from a haploidentical donor between 2010 and 2020 in the EBMT/ALWP registry were selected. A haploidentical donor was defined as ≥2 HLA mismatches between donor and recipient. The exclusion criteria were secondary AML, AML in CR at transplantation, favorable-risk cytogenetics according to the revised 2010 UK-MRC [18], HCT from other donor types (sibling, unrelated, or umbilical cord blood); previous history of HCT; use of ex vivo T-cell–depleted hematopoietic cell graft or use of alemtuzumab or anti thymocyte globulin. Data analyzed included recipient and donor characteristics such as age, gender, cytomegalovirus (CMV) serostatus, and disease-related characteristics such as disease status at transplantation, type of conditioning regimen, stem cell source, and graft-versus-host disease (GVHD) prophylaxis regimen. The conditioning regimen was defined as myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) based on the reports from individual transplantation centers as per previously established criteria [19]. The conditioning regimen was defined as MAC when containing total body irradiation with a dose >6 Gray or a total dose of busulfan >8 mg/kg or >6.4 mg/kg when administered orally or intravenously, respectively. All other regimens were defined as RIC [19]. Regimens for GVHD prophylaxis were per institutional protocol. Grading of acute (a) GVHD was performed using established criteria [20]. Chronic (c) GVHD was classified as limited or extensive according to published criteria [21]. For this study, all necessary data were collected according to the EBMT guidelines, using the EBMT minimum essential data forms. The list of institutions contributing data to this study is provided in the Supplementary appendix.

Ethics Approval and Consent to Participate

The scientific board of the ALWP of the EBMT approved this study. The study protocol was approved by the institutional review board at each site and complied with country-specific regulatory requirements. All patients gave informed consent to use their anonymized personal information for research purposes. The study was conducted according to the Declaration of Helsinki, and Good Clinical Practice guidelines.

Data Sharing Statement

Please contact the EBMT for the raw data used for this study (www.ebmt.org).

Statistical Analysis

The study endpoints were OS, LFS, relapse incidence (RI), non-relapse mortality (NRM), engraftment, aGVHD, cGVHD, and GVHD-free, relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. Median follow-up was calculated using the reverse Kaplan-Meier method. Engraftment was defined as achieving an absolute neutrophil count (ANC) greater than or equal to 0.5×10^9/L for 3 consecutive days. OS was defined as time to death from any cause. LFS was defined as survival with no evidence of relapse or progression. NRM was defined as death from any cause without previous relapse or progression. We used modified GRFS criteria. GRFS events were defined as the first event among grade III–IV acute GVHD, extensive cGVHD, relapse, or death from any other cause [22]. Median values and ranges were used for continuous variables and percentages for categorical variables. Patient-, disease-, and transplant-related characteristics were compared between the 2 groups (intermediate, and high-risk cytogenetics) using the Mann-Whitney *U* test for numerical variables, and the chi-squared or Fisher exact test for categorical variables. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier estimates. The RI and NRM were calculated using cumulative incidence (CI) curves in a competing risk setting, death in remission being treated as a competing event for relapse. Early death was considered as a competing event for engraftment. To

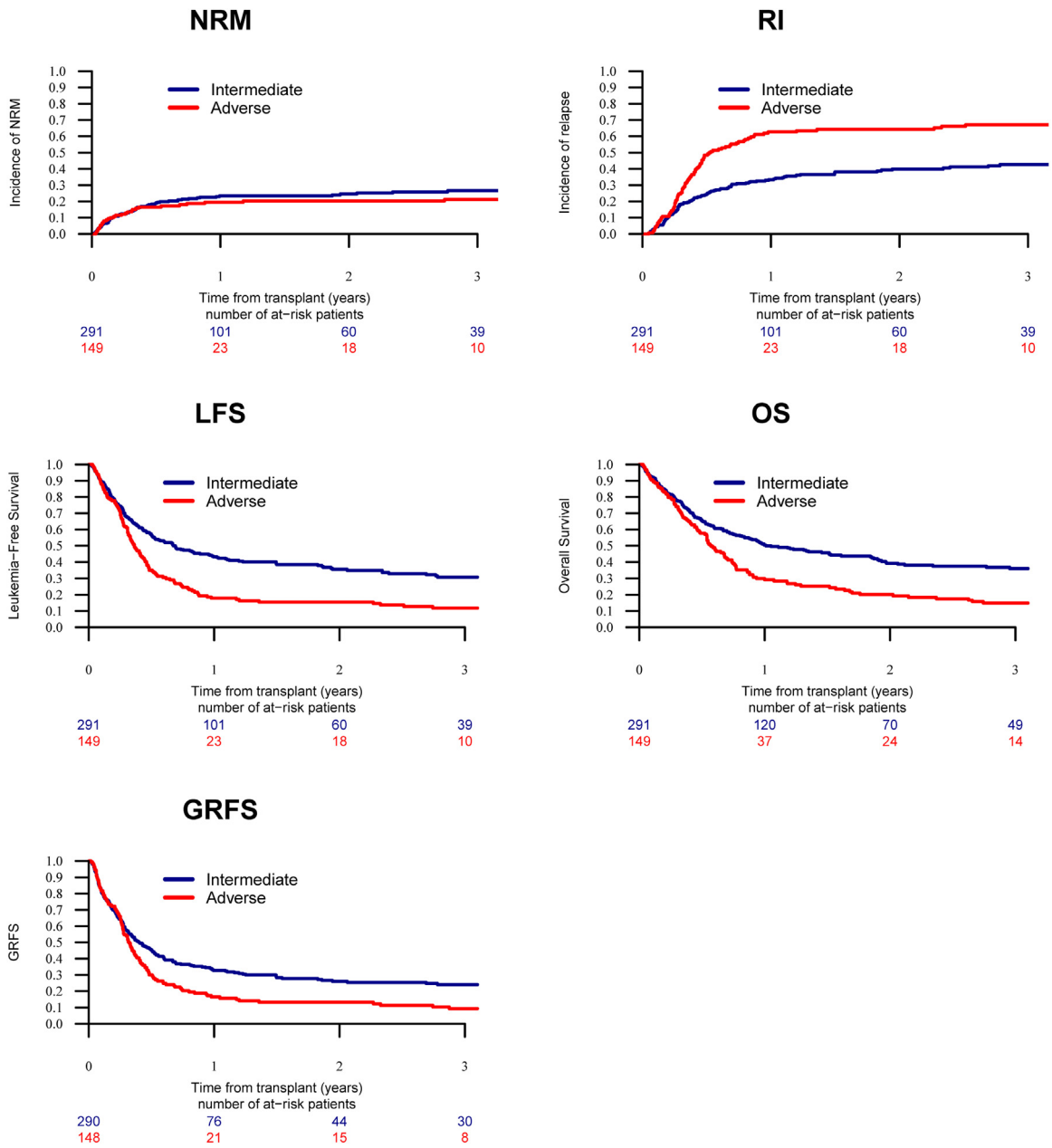

Figure 1. Transplant outcomes.

estimate the CI of acute or chronic GVHD, relapse and death were considered as competing events. Univariate analyses were performed using the log-rank test for LFS, OS, and GRFS whereas Gray's test was used for CI. Multivariate analyses were performed using the Cox proportional-hazards regression model. All variables differing significantly between the two groups, and potential risk factors were included in the model. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). All *P* values were 2-sided with a type 1 error rate fixed at.05. Statistical analyses were performed with SPSS 25.0 (SPSS Inc., Chicago, IL) and R 4.3.0 [23,24].

RESULTS

Patient, Disease, and Transplantation Characteristics

Table 1 shows the baseline characteristics. A total of 440 patients met the inclusion criteria: 291 (66.1%) with intermediate-risk (AMLint) and 149 (44.1%) with adverse-risk cytogenetics (AMLadv). In the AMLadv group, deletion 7 was present in 10.7% of cases, deletion 5 in 2.7%, a complex karyotype was observed in 40.9% of patients, and a monosomal karyotype was present in 13.4% (16.1% fulfilled criteria for both complex and monosomal karyotype). The median duration of follow-up from HCT was 33 (95% CI, 27-44) and 43 (95% CI, 36-60) months, respectively (P = .27). The median year of HCT was 2017 in both subgroups. The median patient age was not statistically different between the two study cohorts being 57.1 years (range 18.1-77.8) in AMLint and 55.6 (range 19.4-72.7) years in AMLadv patients (P = 1.0). There were significant differences between the 2 groups with respect to presence of *FLT3-ITD* which was more frequent among AMLint compared with AMLadv (40.4% and 18.8%, respectively; P = .0006; data available for 62% of cases overall); presence of *NPM1* mutation (AMLint, 42.4% versus AMLadv, 6.9%; $P < .0001$) and the proportion of patients with primary refractory disease (AMLint, 51.9% versus AMLadv, 73.2%; $P < .0001$).

Patient and donor CMV seropositivity was not statistically different between the 2 groups: both AMLint and AMLadv had

Table 1
Baseline Demography According to Cytogenetic Risk Group

	Intermediate (n = 291)	Adverse (n = 149)	Overall (n = 440)	*P* Value
Median follow-up (months, reverse KM), median (95% CI)	33.06 [27.15-43.81]	42.56 [35.69-59.62]	36.12 [32.64-46.28]	.27
Year transplant, median (min-max)	2017 (2010-2020)	2017 (2011-2020)	2017 (2010-2020)	.62
Patient age (y), median (min-max) [IQR]	57.1 (18.1-77.8) [43.6-63.7]	55.6 (19.4-72.7) [45.5-63.4]	56.2 (18.1-77.8) [43.8-63.6]	1
Disease status at transplant				
Primary refractory	151 (51.9%)	109 (73.2%)	260 (59.1%)	<.0001
Rel1	110 (37.8%)	33 (22.1%)	143 (32.5%)	
Rel2+	30 (10.3%)	7 (4.7%)	37 (8.4%)	
Relapse/Refractory				<.0001
Relapse	140 (48.1%)	40 (26.8%)	180 (40.9%)	
Refractory	151 (51.9%)	109 (73.2%)	260 (59.1%)	
Karyotype details				
t(6;9)		2 (1.3%)		
t9;22		3 (2%)		
MLL		8 (5.4%)		
del7/mono7		16 (10.7%)		
del5/mono5		4 (2.7%)		
3q26		8 (5.4%)		
17p		3 (2%)		
CK		61 (40.9%)		
MK		20 (13.4%)		
CK+MK		24 (16.1%)		
Normal karyotype	220 (75.6%)			
Other abnormal	71 (24.4%)			
FLT3-ITD status				.0006
Negative	115 (59.6%)	65 (81.2%)	180 (65.9%)	
Positive	78 (40.4%)	15 (18.8%)	93 (34.1%)	
Missing	62	52	114	
Graft source				.76
BM	94 (32.3%)	46 (30.9%)	140 (31.8%)	
PBSC	197 (67.7%)	103 (69.1%)	300 (68.2%)	
KPS score				.77
<90	126 (45%)	60 (43.5%)	186 (44.5%)	
Missing	11	11	22	
Patient gender: Male	158 (54.3%)	88 (59.1%)	246 (55.9%)	.34
Female donor to male recipient	60 (20.6%)	34 (22.8%)	94 (21.4%)	.59
Patient CMV status				.50
Seropositive	220 (76.4%)	108 (73.5%)	328 (75.4%)	
Missing	3	2	5	
Donor CMV status				.38
Seropositive	170 (60.3%)	81 (55.9%)	251 (58.8%)	
Missing	9	4	13	
Conditioning intensity				.52
MAC	134 (46.2%)	64 (43%)	198 (45.1%)	
RIC	156 (53.8%)	85 (57%)	241 (54.9%)	
Missing	1	0	1	
GVHD prophylaxis in addition to PTCy				.25
CSA	5 (1.7%)	0 (0%)	5 (1.1%)	
MTX	1 (0.3%)	0 (0%)	1 (0.2%)	
Tacro	4 (1.4%)	1 (0.7%)	5 (1.1%)	
MMF	9 (3.1%)	4 (2.7%)	13 (3%)	
CSA + MTX	4 (1.4%)	2 (1.3%)	6 (1.4%)	
CSA + MMF	143 (49.1%)	85 (57%)	228 (51.8%)	
CSA + Tacro	0 (0%)	1 (0.7%)	1 (0.2%)	
CSA + MTX + MMF	0 (0%)	1 (0.7%)	1 (0.2%)	
MMF + Tacro	100 (34.4%)	41 (27.5%)	141 (32%)	
MMF + Siro	18 (6.2%)	10 (6.7%)	28 (6.4%)	

(*continued*)

Table 1 (*Continued*)

	Intermediate (n = 291)	Adverse (n = 149)	Overall (n = 440)	*P* Value
CSA + MMF + Tacro	4 (1.4%)	0 (0%)	4 (0.9%)	
Tacro + Siro	0 (0%)	1 (0.7%)	1 (0.2%)	
Other	3 (1%)	3 (2%)	6 (1.4%)	

KM indicates Kaplan-Meier; KPS, Karnofsky performance status; IQR, interquartile rage; BM, bone marrow; Rel1, first relapse; Rel2+, second or later relapse; CSA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; siro, sirolimus.

a high proportion (76.4% and 73.5 %, respectively) of CMV positivity, as well as a high rate of donor CMV positivity (60.3% and 55.9%, respectively). A MAC regimen was used in 46.2% and 43% of patients in AMLint and AMLadv groups, respectively (P = .52). The HCT graft source was peripheral blood stem cells (PBSC) in most patients (AMLint, 67.7% and AMLadv, 69.1%; P = .76). All patient received PTCy. The majority of patients received either tacrolimus with mycophenolate mofetil (32%) or cyclosporine with mycophenolate mofetil (51.8%) as additional immunosuppression for GVHD prevention. The most common conditioning regimen for both groups was thiotepa/busulfan/fludarabine, used in 42.6% and 43% of AMLint and AMLadv, respectively. A full list of conditioning regimens is provided in Supplementary Table S2.

Transplantation Outcomes

The 2-year relapse, NRM, LFS, OS and GRFS for the entire study population was 48.1%, 23.1%, 28.8%, 32.7%, and 21.7%, respectively (Supplementary Table S3). The proportion of patients who achieved CR after transplant did not differ between the study groups (AMLint, 80.4% versus AMLadv, 72.7% P = .24), with a not statistically different median time to engraftment (19 [range 1-22] versus 19 [range 1-42]) days, respectively (P = .73). Graft failure was reported in 8.6% (AMLint) versus 10.6% (AMLadv) of patients, respectively (P = .51). Supplementary Table S4 describes the univariate outcomes according to patient and donor characteristics. The incidence of grade II-IV (29.1%; 95% CI, 20.6-31.7 and 26.9%; 95% CI, 19.9-34.5) and grade III-IV (12.9%; 95% CI, 9.3-17.1 and 8.5%; 95% CI, 4.6-13.8) aGVHD at day 180 was not statistically different between the study groups. A higher overall cGVHD incidence was observed in AMLint patients (24.4%; 95% CI, 19.2-29.9 and 15.6%; 95% CI, 10-22.3) but not statistically different extensive cGVHD at 2 years in AMLint patients (13.3%; 95% CI, 9.4-17.9 and 8.2%; 95% CI, 3.2-11.6). On the contrary, 2-year RI was lower among AMLint patients (39.9%; 95% CI, 33.8-45.9 versus 64.3%; 95% CI, 55.6-71.7), translating into a superior 2-year LFS (35.5%; 95% CI, 29.5-41.5 versus 15.5%; 95% CI, 9.9-22.1), GRFS (26%; 95% CI, 20.6-31.7 versus 13.2 %; 95% CI, 8.1-19.6) and OS (39.2%; 95% CI, 32.9-45.4 versus 20.1%;95% CI, 13.7-27.4). Two-year NRM (24.6%; 95% CI, 19.6-29.9 versus 20.3%; 95% CI, 14.1-27.3) did not statistically differ between cytogenetic groups. Presence of *FLT3-ITD* was not associated with a higher RI in this study population, with a 2-year RI of 42.5%; 95% CI, 31.8-52.8 versus 50.4%; 95% CI, 42.5-58.2 among patients with and without *FLT3-ITD*, respectively (Supplementary Table S4). Analyzing GVHD as a time dependent variable, we did not find any association with relapse and development of acute or chronic GVHD (Supplementary Table S5). Multivariate analysis (Table 2) confirmed the significantly lower relapse risk in AMLint patients, with an HR = 2.1 (95% CI, 1.57-3.0) for AMLadv patients. Moreover, AMLadv had an independent negative impact on LFS and OS, with HR = 1.71 (95% CI, 1.31-2.22) and HR = 1.69 (95% CI, 1.29-2.22), respectively.

Other factors were identified as having an independent prognostic impact on outcomes in the multivariate analysis. Increasing age was independently associated with a higher risk of NRM, as was a Karnofsky score <90, which predicted a higher NRM and lower LFS, OS, and GRFS. Donor CMV positivity was associated with a higher relapse risk, as well as an inferior LFS, OS, and GRFS. Disease status before transplant (primary refractory versus relapsed) or conditioning intensity (RIC versus MAC) did not influence any transplant outcomes in our regression model. Finally, the use of PBSC was associated with a marked higher incidence of grade II-IV aGVHD (Table 2). In subgroup analysis, transplant outcomes were comparable between patients with primary refractory and relapsed AML (data now shown). Moreover, there was no significant interaction between cytogenetics and status at transplant in multivariate analysis.

Cause of Death

Table 3 details the cause of death. A total of 288 (65.5%) patients died during the study period, comprising 170 (58.4%) and 118 (79.2%) of the AMLint and AMLadv cohorts, respectively. Disease relapse, infection, and GVHD were the most common causes of death in both cohorts, accounting for 54.9%, 21.6%, and 14.2% of deaths among AMLint patients, and 60.4%, 17.5%, and 10% of the AMLadv cohort, respectively.

DISCUSSION

In the current study we addressed the impact of cytogenetic risk on transplantation outcome of AML patients with active disease undergoing haplo-HCT. Our results indicate that cytogenetic risk, despite not influencing initial post-transplantation response, had an important independent prognostic impact on relapse risk, which translated into an inferior LFS and OS in those with adverse risk cytogenetics. These results are comparable to the well-known effect of cytogenetics in patients with AML undergoing allogeneic transplantation in remission, as well as after allo-HCT performed in active disease from a matched sibling or unrelated donor [13,15-17,25]. Among AMLadv patients, the RI surpassed 60% and the OS was 20% at 2 years after haplo-HCT, highlighting the need for novel strategies to improve the outcomes of these patients [26].

Cytogenetics exerts a strong impact on outcome of patients with AML, predicting response to initial chemotherapy and risk of relapse. Accordingly, cytogenetic risk profile constitutes one of the main criteria guiding risk-adapted indication for HCT [27,28]. Nonetheless, adverse cytogenetics maintains its deleterious prognostic impact in patients undergoing allo-HCT. The CIBMTR studied 821 patients with AML in first or second CR who underwent HCT demonstrating the predictive value of cytogenetic risk, with a 5-year OS of only 18% in the adverse-risk cytogenetic category, in comparison to a 5-year OS of 50% in those classified as intermediate-risk [15]. Moreover, the ALWP have analyzed the prognostic impact of several cytogenetic abnormalities on transplant outcome and has shown the poor prognosis of patients with cytogenetic subtypes such as AML with del(5q)/−5, or with −7, or with 17p abnormalities, especially when part of a complex karyotype [25,29-31]. Most patients classified as adverse risk in the

Table 2
Multivariate Analysis of Transplant Outcomes

Variables*	Relapse		NRM		LFS		OS		GRFS		Acute GVHD, Grade II-IV		Chronic GVHD	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Intermediate risk cytogenetics	1		1		1		1		1		1		1	
Adverse risk cytogenetics	2.17 (1.57-3)	<.0001	1.1 (0.7-1.74)	.67	1.71 (1.31-2.22)	<.0001	1.69 (1.29-2.22)	.0001	1.37 (1.06-1.77)	.016	0.89 (0.58-1.38)	.62	0.97 (0.56-1.69)	.92
Patient age (per 10 years increment)	0.91 (0.8-1.02)	.12	1.43 (1.16-1.76)	.0007	1.04 (0.94-1.15)	.45	1.1 (0.99-1.22)	.088	1.03 (0.94-1.14)	.51	1.05 (0.89-1.23)	.58	0.92 (0.77-1.1)	.36
Year of transplantation	0.94 (0.87-1)	.065	1.02 (0.92-1.12)	.76	0.96 (0.91-1.02)	.18	0.99 (0.93-1.05)	.63	0.98 (0.93-1.04)	.51	1.01 (0.92-1.11)	.84	1.03 (0.93-1.14)	.60
Relapsed	1		1		1		1		1		1		1	
Primary refractory	1.03 (0.74-1.42)	.87	0.96 (0.62-1.48)	.86	1.02 (0.78-1.32)	.89	1.01 (0.77-1.33)	.95	1.02 (0.79-1.31)	.90	1.13 (0.74-1.72)	.58	0.76 (0.47-1.22)	.25
MAC	1		1		1		1		1		1		1	
RIC	1.1 (0.78-1.56)	.59	0.99 (0.61-1.61)	.96	1.11 (0.83-1.48)	.49	1.13 (0.84-1.53)	.41	0.94 (0.71-1.24)	.66	1.06 (0.68-1.68)	.79	0.96 (0.57-1.59)	.87
KPS <90	1		1		1		1		1		1		1	
KPS ≥90	0.66 (0.48-0.9)	.01	0.52 (0.34-0.79)	.002	0.6 (0.47-0.77)	<.0001	0.6 (0.46-0.78)	.0001	0.62 (0.49-0.79)	.0001	1.2 (0.8-1.82)	.38	0.71 (0.44-1.14)	.16
Female donor to male recipient	1.14 (0.8-1.63)		1.27 (0.79-2.05)		1.17 (0.88-1.56)		1.3 (0.97-1.74)		1.23 (0.93-1.63)		0.93 (0.58-1.5)		1.21 (0.71-2.06)	
Donor CMV seronegative	1		1		1		1		1		1		1	
Donor CMV seropositive	1.27 (0.9-1.79)	.17	0.71 (0.45-1.12)	.14	1.04 (0.79-1.37)	.79	1.05 (0.79-1.4)	.71	1.02 (0.79-1.33)	.86	1.51 (0.95-2.41)	.081	1.4 (0.81-2.42)	.22
Patient CMV seronegative	1		1		1		1		1		1		1	
Patient CMV seropositive	1.03 (0.69-1.54)	.87	1.28 (0.75-2.19)	.37	1.08 (0.78-1.49)	.63	1.15 (0.82-1.61)	.42	0.94 (0.69-1.27)	.67	0.69 (0.42-1.15)	.16	0.6 (0.33-1.07)	.083
BM graft	1		1		1		1		1		1		1	
PBSC graft	1.04 (0.73-1.48)	.84	0.99 (0.62-1.57)	.96	1 (0.75-1.33)	.97	0.98 (0.73-1.31)	.88	1.06 (0.8-1.4)	.69	1.95 (1.15-3.32)	.013	1.3 (0.76-2.23)	.33

* Variables differing between the study cohorts and factors associated with at least 1 outcome in the univariate analysis.

Table 3
Cause of Death

Etiology	Intermediate (n = 170)	Adverse (n = 118)	Overall (n = 288)
Original disease	89 (54.9%)	169 (60.4%)	80 (67.8%)
Infection	35 (21.6%)	49 (17.5%)	14 (11.9%)
GVHD	23 (14.2%)	28 (10%)	5 (4.2%)
Hemorrhage	1 (0.6%)	3 (1.1%)	2 (1.7%)
Failure/Rejection	0 (0%)	2 (0.7%)	2 (1.7%)
Veno-occlusive disease	1 (0.6%)	2 (0.7%)	1 (0.8%)
Interstitial pneumonitis	3 (1.9%)	5 (1.8%)	2 (1.7%)
Other second malignancy	0 (0%)	2 (0.7%)	2 (1.7%)
Multiorgan failure	3 (1.9%)	7 (2.5%)	4 (3.4%)
Other transplant related	4 (2.5%)	4 (1.4%)	0 (0%)
Non-transplant related	3 (1.9%)	9 (3.2%)	6 (5.1%)
Missing	8	8	0

present series carried one of these very high-risk cytogenetic aberrations (Table 1).

However, the role of cytogenetic risk on transplantation outcome in patients who undergo transplantation with active disease (R/R AML) is not so clearly established. Long-term survival of refractory patients undergoing allo-HCT is approximately 25% to 30% [9,25,30,32], although well-established predictors of sustained response after allo-HCT in this setting are mostly unknown [3,29-31,33]. We recently addressed, in the EBMT registry, the impact of cytogenetic risk in patients with R/R AML undergoing transplantation from HLA-matched donors and demonstrated that karyotype remains an important prognostic factor in this context [17]. Haplo-HCT may provide important advantages in the setting of active disease, including the relatively shorter time to graft procurement compared to a registry-donor [34], a hypothetical stronger GVL effect because of the broader HLA disparity [35], and the shorter period of post-transplantation immunosuppression when using PTCy as GVHD prophylaxis [36]. Nonetheless, we demonstrated that adverse cytogenetics is associated with a higher relapse rate, approaching 64% at 2 years in the current study, indicating that haplo-HCT may not overcome the deleterious effect of adverse-risk cytogenetics as seen with other allogeneic transplantation modalities. Furthermore, the higher relapse rate in patients with adverse cytogenetics translated to lower LFS and OS, altogether highlighting the need for additional antileukemic procedures after Haplo-HCT, either pharmacological or cell-therapy based strategies, aimed at preventing relapse. On the contrary, cytogenetic risk did not influence NRM, incidence of GVHD and other transplant outcome parameters in agreement with previous studies [12–17]. The outcomes of primary refractory or relapsed AML remain poor with median survival less than 6 months in most patients without consolidative transplant [37]. In various retrospective studies, CR rates with intensive salvage chemotherapy in relapsed/refractory AML are in the range of 20% to 40% [38]. Our results support the use of haplo-HCT in eligible patients with active AML because it can achieve high CR rates and durable remissions in a subset of patients.

Consistent with other studies, we confirmed the prognostic impact of other variables with transplant outcome, such as correlation of increasing age and of KPS with NRM, donor CMV sero-positivity and transplant outcome, use of PBSC and GVHD incidence, and the protective role of PTCy on cGVHD incidence, without influencing disease relapse and favoring a higher GRFS [5,8-11,39-43].

Being registry based, our study suffers from several limitations including the lack of complete genomic information at diagnosis, details on upfront chemotherapy protocols and the precise percentage of blasts at time of transplantation. We also did not have information post-transplant maintenance therapies in the database. Nevertheless, we were able to demonstrate that cytogenetic risk remains an important prognostic factor in R/R AML with active disease before non-T-cell–depleted HCT mainly because of a very high relapse risk, warranting the implementation of innovative additional antileukemic pharmacologic or cellular therapies after transplantation.

ACKNOWLEDGMENTS

We thank all the European Society for Blood and Marrow Transplantation (EBMT) centers and national registries for contributing patients to this study (Appendix of Supplementary Tables). We also thank the data managers for their excellent work and the patients who contributed their data.

Presented as a poster abstract at Annual European Bone Marrow Transplantation (EBMT) meeting, Virtual, 24th June, 2021.

Financial disclosure: Nothing to report.

Conflict of interest statement: J.P. reports grant of Ministry of Health of the Czech Republic – Conceptual Development of Research Organization (Faculty Hospital in Pilsen - FNPI, 00669806).

Authorship statement: A.N., M.M., and M.L. contributed to the conception and design of the study. M.L. analyzed the data. A.N., B.D., B.N.S., M.L., M.M. contributed to the writing of the manuscript. All authors critically reviewed the manuscript and approved the final version.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.08.018.

REFERENCES

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med*.. 2015;373:1136–1152.
2. Pulte D, Jansen L, Brenner H. Changes in long term survival after diagnosis with common hematologic malignancies in the early 21st century. *Blood Cancer J*. 2020;10(5):56.
3. Schlenk RF, Frech P, Weber D, et al. Impact of pretreatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia. *Leukemia*. 2017;31:1217–1220.
4. Thol F, Ganser A. Treatment of relapsed acute myeloid leukemia. *Curr Treat Options Oncol*. 2020;21(8):66.

5. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2017;52:811–817.
6. Cytryn S, Abdul-Hay M. Haploidentical hematopoietic stem cell transplantation followed by "post-cyclophosphamide": the future of allogeneic stem cell transplant. *Clin Hematol Int*. 2020;2:49–58.
7. Shouval R, Fein JA, Labopin M, et al. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. *Lancet Haematol*. 2019;6(11):e573–e584.
8. Nagler A, Savani BN, Labopin M, et al. Outcomes after use of two standard ablative regimens in patients with refractory acute myeloid leukaemia: a retrospective, multicentre, registry analysis. *Lancet Haematol*. 2015;2(9):e384–e392.
9. Brissot E, Labopin M, Ehninger G, et al. Haploidentical versus unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: a report on 1578 patients from the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2019;104:524–532.
10. Battipaglia G, Boumendil A, Labopin M, et al. Unmanipulated haploidentical versus HLA-matched sibling allogeneic hematopoietic stem cell transplantation in relapsed/refractory acute myeloid leukemia: a retrospective study on behalf of the ALWP of the EBMT. *Bone Marrow Transplant*. 2019;54:1499–1510.
11. Bazarbachi A, Schmid C, Labopin M, et al. Evaluation of trends and prognosis over time in patients with AML relapsing after allogeneic hematopoietic cell transplant reveals improved survival for young patients in recent years. *Clin Cancer Res*. 2020;26:6475–6482.
12. Cornelissen JJ, Breems D, van Putten WL, et al. Comparative analysis of the value of allogeneic hematopoietic stem-cell transplantation in acute myeloid leukemia with monosomal karyotype versus other cytogenetic risk categories. *J Clin Oncol*. 2012;30:2140–2146.
13. Medeiros BC, Othus M, Fang M, Appelbaum FR, Erba HP. Cytogenetic heterogeneity negatively impacts outcomes in patients with acute myeloid leukemia. *Haematologica*. 2015;100:331–335.
14. Ciurea SO, Labopin M, Socie G, et al. Relapse and survival after transplantation for complex karyotype acute myeloid leukemia: a report from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation and the University of Texas MD Anderson Cancer Center. *Cancer*.. 2018;124:2134–2141.
15. Armand P, Kim HT, Zhang MJ, et al. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. *Biol Blood Marrow Transplant*. 2012;18:280–288.
16. Canaani J, Labopin M, Itälä-Remes M, Blaise D, Socié G, Forcade E, et al. Prognostic significance of recurring chromosomal abnormalities in transplanted patients with acute myeloid leukemia. *Leukemia*. 2019;33:1944–1952.
17. Poiani M, Labopin M, Battipaglia G, et al. The impact of cytogenetic risk on the outcomes of allogeneic hematopoietic cell transplantation in patients with relapsed/refractory acute myeloid leukemia: On behalf of the acute leukemia working party (ALWP) of the European group for blood and marrow transplantation (EBMT). *Am J Hematol*. 2021;96:40–50.
18. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116:354–365.
19. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628–1633.
20. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
21. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69:204–217.
22. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51:610–611.
23. Kanate AS, Nagler A, Savani B. Summary of scientific and statistical methods, study endpoints and definitions for observational and registry-based studies in hematopoietic cell transplantation. *Clin Hematol Int*. 2019;2:2–4.
24. *R: A language and environment for statistical computing*. Vienna: R Core Team: R Foundation for Statistical Computing; 2020.
25. Halaburda K, Labopin M, Houhou M, et al. AlloHSCT for inv(3)(q21;q26)/t(3;3)(q21;q26) AML: a report from the acute leukemia working party of the European society for blood and marrow transplantation. *Bone Marrow Transplant*. 2018;53:683–6891.
26. Culos K, Byrne M. Salvage therapy after allogeneic hematopoietic cell transplantation: targeted and low-intensity treatment options in myelodysplastic syndrome and acute myeloid leukemia. *Clin Hematol Int*. 2019;1:94–100.
27. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447.
28. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31:697–712.
29. Poiré X, Labopin M, Maertens J, et al. Allogeneic stem cell transplantation in adult patients with acute myeloid leukaemia and 17p abnormalities in first complete remission: a study from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). *J Hematol Oncol*. 2017;10:20.
30. Poiré X, Labopin M, Polge E, et al. Allogeneic stem cell transplantation using HLA-matched donors for acute myeloid leukemia with deletion 5q or monosomy 5: a study from the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2020;105:414–423.
31. Poiré X, Labopin M, Polge E, et al. The impact of concomitant cytogenetic abnormalities on acute myeloid leukemia with monosomy 7 or deletion 7q after HLA-matched allogeneic stem cell transplantation. *Am J Hematol*. 2020;95:282–294.
32. 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*. 2000;96:4075–4083.
33. Nagler A, Savani BN, Labopin M, et al. Outcomes after use of two standard ablative regimens in patients with refractory acute myeloid leukaemia: a retrospective, multicentre, registry analysis. *Lancet Haematol*. 2015;2(9):e384–e392.
34. Champlin R. Is unrelated donor or haploidentical hematopoietic transplantation preferred for patients with acute myeloid leukemia in remission? *Haematologica*. 2020;105:252–254.
35. Guo H, Chang Y-J, Hong Y, et al. Dynamic immune profiling identifies the stronger graft-versus-leukemia (GVL) effects with haploidentical allografts compared to HLA-matched stem cell transplantation. *Cell Mol Immunol*. 2021;18:1172–1185.
36. Tegla C, Choi J, Abdul-Hay M, Cirrone F, Cole K, Al-Homsi AS. Current status and future directions in graft-versus-host disease prevention following allogeneic blood and marrow transplantation in adults. *Clin Hematol Int*. 2020;2:5–12.
37. Ferguson P, Hills RK, Grech A, et al. An operational definition of primary refractory acute myeloid leukemia allowing early identification of patients who may benefit from allogeneic stem cell transplantation. *Haematologica*. 2016;101:1351–1358.
38. Wattad M, Weber D, Döhner K, et al. Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. *Leukemia*. 2017;31:1306–1313.
39. Bazarbachi A, Labopin M, Blaise D, et al. Comparable outcomes of haploidentical transplant with TBF conditioning versus matched unrelated donor with fludarabine/busulfan conditioning for acute myeloid leukemia. *Bone Marrow Transplant*. 2021;56:622–634.
40. Sanz J, Galimard JE, Labopin M, et al. Post-transplant cyclophosphamide after matched sibling, unrelated and haploidentical donor transplants in patients with acute myeloid leukemia: a comparative study of the ALWP EBMT. *J Hematol Oncol*. 2020;13:46.
41. Ruggeri A, Sun Y, Labopin M, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin as graft- versus-host disease prophylaxis in haploidentical transplant. *Haematologica*. 2017;102:401–410.
42. Ruggeri A, Labopin M, Bacigalupo A, et al. Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. *Cancer*. 2018;124:1428–1437.
43. Crocchiolo R, Castagna L, Furst S, et al. The patient's CMV serological status affects clinical outcome after T-cell replete haplo-HSCT and post-transplant cyclophosphamide. *Bone Marrow Transplant*. 2016;51:1134–1136.