Allogeneic stem cell transplantation benefits for patients ≥ 60 years with acute myeloid leukemia and FLT3 internal tandem duplication:

Poiré, Xavier; Labopin, Myriam; Polge, Emmanuelle; Passweg, Jakob; Craddock, Charles; Blaise, Didier; Cornelissen, Jan J.; Volin, Liisa; Russell, Nigel H.; Socié, Gérard; Michallet, Mauricette; Fegueux, Nathalie; Chevallier, Patrice; Brecht, Arne; Hunault-Berger, Mathilde; Mohty, Mohamad; Esteve, Jordi; Nagler, Arnon

DOI:
10.3324/haematol.2017.178251

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Poiré, X, Labopin, M, Polge, E, Passweg, J, Craddock, C, Blaise, D, Cornelissen, JJ, Volin, L, Russell, NH, Socié, G, Michallet, M, Fegueux, N, Chevallier, P, Brecht, A, Hunault-Berger, M, Mohty, M, Esteve, J & Nagler, A 2018, 'Allogeneic stem cell transplantation benefits for patients ≥ 60 years with acute myeloid leukemia and FLT3 internal tandem duplication: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation', *Haematologica*, vol. 103, no. 2, pp. 256-265. https://doi.org/10.3324/haematol.2017.178251

Allogeneic stem cell transplantation benefits for patients ≥ 60 years with acute myeloid leukemia and *FLT3* internal tandem duplication: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Xavier Poiré,[1] Myriam Labopin,[2,3] Emmanuelle Polge,[2,3] Jakob Passweg,[4] Charles Craddock,[5] Didier Blaise,[6] Jan J. Cornelissen,[7] Liisa Volin,[8] Nigel H. Russell,[9] Gérard Socié,[10] Mauricette Michallet,[11] Nathalie Fegueux,[12] Patrice Chevallier,[13] Arne Brecht,[14] Mathilde Hunault-Berger,[15] Mohamad Mohty,[2,3*] Jordi Esteve[16*] and Arnon Nagler[2,17*]

[1]Section of Hematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [2]Acute Leukemia Working Party of the EBMT; [3]Service d'Hématologie, Hôpital Saint-Antoine, Paris, France; [4]Hematology, University Hospital, Basel, Switzerland; [5]Center for Clinical Haematology, Queen Elizabeth Hospital, Birmingham, UK; [6]Programme de Transplantation et Thérapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, France; [7]Daniel den Hoed Cancer Centre, Erasmus Medical Center, Rotterdam, the Netherlands; [8]Stem Cell Transplantation Unit, HUH Comprehensive Cancer Center, Helsinki, Finland; [9]Nottingham City Hospital, UK; [10]Department of Hematology, Hôpital Saint-Louis, Paris, France; [11]Service Hématologie, Centre Hospitalier Lyon Sud, France; [12]Département d'Hématologie Clinique, CHU Lapeyronie, Montpellier, France; [13]Département d'Hématologie, CHU Nantes, France; [14]Deutsche Klinik für Diagnostik, KMT Zentrum, Wiesbaden, Germany; [15]Service des Maladies du Sang, CHRU, Angers, France; [16]Hematology Department, IDIBAPS, Hospital Clinic, Barcelona, Spain and [17]Chaim Sheba Medical Center, Tel-Hashomer, Israel '

*MM, JE and AN contributed equally to this work

Haematologica 2018
Volume 103(2):256-265

Correspondence:
xavier.poire@uclouvain.be

Received: August 8, 2017.
Accepted: December 7, 2017.
Pre-published: December 14, 2017.

doi:10.3324/haematol.2017.178251

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/103/2/256

ABSTRACT

Intermediate-risk cytogenetic acute myeloid leukemia with an internal tandem duplication of *FLT3* (*FLT3*-ITD) is associated with a high risk of relapse, and is now a standard indication for allogeneic stem cell transplantation. Nevertheless, most studies supporting this strategy have been performed in young patients. To address the benefit of allogeneic transplantation in the elderly, we made a selection from the European Society for Blood and Marrow Transplantation registry of *de novo* intermediate-risk cytogenetic acute myeloid leukemia harboring *FLT3*-ITD in patients aged 60 or over and transplanted from a related or unrelated donor between January 2000 and December 2015. Two hundred and ninety-one patients were identified. Most patients received a reduced-intensity conditioning (82%), while donors consisted of an unrelated donor in 161 (55%) patients. Two hundred and twelve patients received their transplantation in first remission, 37 in second remission and 42 in a more advanced stage of the disease. The 2-year leukemia-free survival rate was 56% in patients in first remission, 22% in those in second remission and 10% in patients with active disease, respectively ($P<0.005$). Non-relapse mortality for the entire cohort was 20%. In multivariate analysis, disease status at transplantation was the most powerful predictor of worse leukemia-free survival, graft-*versus*-host disease and relapse-free survival, and overall survival. In this elderly population, age was not associated with outcome. Based on the current results, allogeneic transplantation translates into a favorable outcome in fit patients ≥ 60 with *FLT3*-ITD acute myeloid leukemia in first remission, similarly to current treatment recommendations for younger patients.

Introduction

Internal tandem duplication in the juxtamembrane domain of the tyrosine kinase receptor gene *FLT3* (*FLT3*-ITD) is one of the most frequent recurrent mutations in acute myeloid leukemia (AML),[1-3] and translates into early relapse and worse sur-

vival in young and older AML patients with normal karyotype or other intermediate-risk cytogenetics (IRC).[4-6] Allogeneic stem cell transplantation (SCT), which has been shown to be beneficial in first remission (CR1) in most studies,[3,7-11] has emerged as the best consolidation strategy in these patients. However, the vast majority of these studies were performed in patients under 60 years of age, transplanted with a myeloablative conditioning and using a matched sibling donor, while data for SCT in patients over 60 years of age harboring *FLT3*-ITD AML in CR1, especially with a reduced-intensity conditioning (RIC) regimen, are rather limited.

The benefit of RIC SCT in AML patients with *FLT3*-ITD in CR1 has been observed in a previously reported small-scale single center study.[12] Howbeit, the median age in this study was 55, ranging from 19 to 64 years, which may not represent a true elderly population. In a subsequent retrospective European Society for Blood and Marrow Translation (EBMT) study by Schmid *et al.*, the authors confirmed the significant negative impact of *FLT3*-ITD on outcome.[13] Moreover, in this cohort, which included patients of up to 71 years old, advanced age was found to be a significant negative factor, associated with worse leukemia-free survival (LFS) and increased non-relapse mortality (NRM).[3,13] Nevertheless, the improvement in supportive care, human leukocyte antigen (HLA) typing and the development of new RIC regimens substantially reduce NRM, extend the eligibility criteria for SCT, and signify that age should no longer be a barrier to SCT.[14,15] Albeit, relapse remains the major cause of treatment failure with RIC regimens.[16,17] Due to the early relapse incidence (RI) in *FLT3*-ITD AML[4] and the intrinsic chemoresistance and poor tolerance to therapy in elderly patients,[18] the role of SCT in this older population may appear questionable. To evaluate the potential benefit of SCT in elderly patients with *FLT3*-ITD AML, we decided to conduct a retrospective study based on the EBMT registry in order to address the outcomes of *FLT3*-ITD AML in patients aged 60 or over and undergoing SCT.

Methods

Patient selection and data collection

Herein is a retrospective study performed by the Acute Leukemia Working Party (ALWP) of the EBMT group. The EBMT registry is a voluntary working group of more than 500 transplant centers, the participants of which are required to report all consecutive SCT and follow-up from their respective centers once a year. Patients aged 60 or over with a diagnosis of *de novo* AML transplanted between 1st January 2000 and 31st December 2015 with a related or unrelated donor (10/10 or 9/10) who were reported to the EBMT registry were included in this analysis. We selected only those patients with normal karyotype or other intermediate-risk karyotype. according to the European LeukemiaNet (ELN) classification,[19,20] and harboring a *FLT3*-ITD mutation at the time of diagnosis. Patients with second SCT have been excluded, as have those who underwent a cord blood or haploidentical transplantation. All patients provided informed consent for the use of their data in retrospective studies. The Review Board of the ALWP as well as the ethic committee of the EBMT approved this study. A total of 291 patients from 100 centers met the criteria and were selected for further analysis.

Myeloablative conditioning (MAC), RIC and non-myeloablative conditioning regimen (NMA) have been defined elsewhere.[21] The following variables were selected and included in the analysis: year of transplantation, age, sex, white blood cell count (WBC) at diagnosis, status at transplantation, time from diagnosis to CR, time from CR to SCT, the number of induction courses to reach CR, type of conditioning regimen, *in vivo* T-cell depletion (including both anti-thymocyte globulins and alemtuzumab), cytomegalovirus (CMV) status of donor and recipient, donor type, source of stem cells, Karnofsky performance status (KPS) at transplantation, engraftment, presence of acute and chronic graft-*versus*-host disease (GvHD), grade of acute GvHD, and NPM1 status. The molecular remission status at the time of SCT is center-dependent and was not defined in the registry.

Statistical analysis and endpoints definitions

Endpoints included LFS, RI, NRM, overall survival (OS), acute and chronic GvHD, and GvHD-free/relapse-free survival (GRFS). All outcomes were measured from the time of transplant. LFS was defined as survival without relapse; patients alive without relapse were censored at the time of last contact. OS was based on death from any cause. NRM was defined as death without previous relapse. GRFS was defined as survival without grade 3-4 acute GvHD, extensive chronic GvHD, relapse or death. Surviving patients were censored at the time of last contact. The probabilities of OS, LFS and GRFS were calculated by the Kaplan-Meier test, and those of acute and chronic GvHD, NRM, and relapse were determined by the cumulative incidence estimator to accommodate competing risks. Results are expressed with a 95% confidence interval (CI). For NRM, relapse was the competing risk, while for relapse the competing risk was NRM. For acute and chronic GvHD, death without the event and relapse were the competing risks.

For all prognostic analyses, continuous variables were categorized and the median was used as a cut-off point, excepting that of age which was analyzed as a continuous variable in multivariate analysis. A Cox proportional hazards model was used for multivariate regression. Factors associated with a *P*-value less than 0.15 by univariate analysis, and other clinically meaningful variables were included in the model. Results were expressed as the hazard ratio (HR) with 95% CI.

All tests were two-sided. The type-1 error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 19 (SPSS Inc./IBM, Armonk, NY, USA) and R 3.0.1 (R Development Core Team, Vienna, Austria) software packages.

Results

Patients' characteristics

Characteristics of the 291 selected patients are listed in Table 1. Median age at SCT was 63.7 years (range: 60-75.4). Only 12 patients were over 70 years old. The most frequent RIC was fludarabine and busulfan (N=118), followed by fludarabine and melphalan (N=42). Twenty-three patients, including 15 with active disease, one in second complete remission (CR2) and seven in CR1, received a fludarabine, amsacrine, and cytarabine (FLAMSA)-RIC preparative regimen.[22] *In vivo* T-cell depletion (TCD) included 162 patients with anti-thymocyte globulins and 35 patients with alemtuzumab. At the time of SCT, most patients (252, 94%) had a KPS of more than 80%, and 71% had more than 90%. The characteristics of CR1 patients are summarized in Table 2. Molecular status at the time of SCT was available for 104 out of 202 CR1 patients; 80 (77%) were in molecular CR1.

Engraftment and graft-*versus*-host disease

Engraftment was successful in 268 patients (98%) with a median time to neutrophils engraftment of 17 days (range: 6-64). The cumulative incidence of grade II-IV acute GvHD was 22% (95% CI: 17.7-27.6) and the 2-year cumulative incidence of chronic GvHD was 34% (95% CI: 28.4-40.5) (Figure 1). The cumulative incidence of grade III-IV acute GvHD was 8% (95% CI: 5-12) and the 2-year cumulative incidence of extensive chronic GvHD was 15% (95% CI: 10.5-19.8).

In the multivariate analysis performed in the entire population, a lower performance status was associated with more grade III-IV acute GvHD (16% [95% CI: 8.2-25.2] *vs.* 6% [95% CI: 3.2-6.2], for patients with KPS of <90% *vs.* ≥90%, respectively, HR=0.4, 95% CI: 0.17-0.93, *P*=0.03). The age of both the patient and donor, type of donor, source of stem cells, TCD and conditioning intensity were

Table 1. Patient characteristics of the entire cohort.

	Patient's characteristics N=291
Median age at SCT (range)	63.7 years old (60-75.4)
Median follow-up (range)	23 months (2-173)
WBC at diagnosis (range)	44.0 x 10⁹/L (1-575)
Median year of SCT	2012 (2002-2015)
Remission status at SCT, N(%)	
CR1	212 (72.9%)
CR2	37 (12.7%)
Not in CR	42 (14.4%)
Sex, N(%)	
Male	150 (51.5%)
Female	141 (48.5%)
Donor type, N(%)	
Sibling	130 (44.7%)
Unrelated	161 (55.3%)
Cytogenetics, N(%)	
Normal	254 (87.3%)
Abnormal	37 (12.7%)
NPM1 status, N(%)	
Unmutated	50 (24.6%)
Mutated	153 (75.4%)
Missing	88
Source of SC	
BM	27 (9.3%)
PB	264 (90.7%)
In vivo T-cell depletion, N(%)	197 (68.4%)
Conditioning regimen, N(%)	
MAC	52 (17.9%)
RIC	200 (68.7%)
NMA	39 (13.4%)
Karnofsky > 80%, N(%)	252 (94%)
CMV patient+, N(%)	199 (69%)
CMV donor+, N(%)	153 (53.3%)
Co-morbidity score (HCT-CI)	
0	65 (58%)
1-2	22 (19.6%)
3+	25 (22.3%)
Missing	179

N: number; SCT: stem cell transplantation; WBC: white blood cell count; CR: complete remission; SC: stem cell; BM: bone marrow; PB: peripheral blood; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; NMA: non myeloablative conditioning; CMV: cytomegalovirus; HCT-CI: hematopoietic cell transplant co-morbidity index.

Table 2. CR1 patients' characteristics.

	Patient's characteristics N=212
Median age at SCT (range)	63.5 years old (60-72.4)
WBC at diagnosis (range)	42.3 x 10⁹/L (1-380)
Median year of SCT	2012 (2002-2015)
Interval from diagnosis to CR1 (range)	42 days (13-149)
Interval from CR1 to SCT (range)	98 days (15-300)
Interval from diagnosis to SCT (range)	5 months (2-17)
Number of induction courses to CR1, N(%)	
1	126 (73.7%)
2 or more	45 (26.3%)
Missing	41
Sex , N(%)	
Male	110 (51.9%)
Female	102 (48.1%)
Female to male, N(%)	41 (19.3%)
Donor type, N(%)	
Sibling	103 (48.6%)
Unrelated	109 (51.4%)
Cytogenetics, N(%)	
Normal	183 (86.3%)
Abnormal	29 (13.7%)
NPM1 status, N(%)	
Unmutated	35 (23.5%)
Mutated	114 (76.5%)
Missing	63
Molecular CR at SCT	
No molecular CR	24 (23.1%)
Molecular CR	80 (76.9%)
Missing	108
Source of SC	
BM	23 (10.9%)
PB	189 (89.2%)
In vivo T-cell depletion, N(%)	142 (67.6%)
Conditioning regimen, N(%)	
MAC	33 (15.6%)
RIC	146 (68.9%)
NMA	33 (15.6%)
Karnofsky > 80%, N(%)	186 (96.4%)
CMV patient+, N(%)	140 (66.4%)
CMV donor+, N(%)	114 (54.3%)
Co-morbidity score (HCT-CI)	
0	47 (57.3%)
1-2	18 (22%)
3+	17 (20.7%)
Missing	130

N: number; SCT: stem cell transplantation; WBC: white blood cell count; CR1: first complete remission; SC: stem cell; BM: bone marrow; PB: peripheral blood; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; NMA: non myeloablative conditioning; CMV: cytomegalovirus; HCT-CI: hematopoietic cell transplant co-morbidity index.

not significantly associated with the incidence of acute GvHD. Focusing on the 212 patients transplanted in CR1, only a better KPS (>90%) at SCT correlated with less grade II-IV and grade III-IV acute GvHD (HR=0.43, 95% CI: 0.22-0.82, *P*=0.01 and HR=0.13, 95% CI: 0.04-0.41, *P*=0.0005, respectively).

Regarding chronic GvHD, no correlation was observed between the cumulative incidence of chronic GvHD and age, type of donor or source of stem cells. In the multivariate analysis performed in the entire population, better KPS was associated with more overall chronic GvHD (HR=1.95, 95% CI: 1.08-3.51, *P*=0.03), while TCD correlated with less overall chronic GvHD (HR=0.51, 95% CI: 0.32-0.83, *P*=0.006) and less extensive chronic GvHD (HR=0.29, 95% CI: 0.14-0.59, *P*<0.001). We also found significantly less extensive chronic GvHD with RIC (*P*=0.02), and more extensive chronic GvHD with a female donor to a male recipient (*P*=0.02). Among patients transplanted in CR1, we found a significant impact of donor's age, with a higher incidence of chronic GvHD when an older donor was used (46% [95% CI: 35-56.9] *vs.* 31% [95% CI: 21.5-41.7] with a donor aged >47 and ≤47 years old, respectively, *P*=0.04).

Non-relapse mortality

The 2-year cumulative incidence of NRM for the whole cohort was 20% (95% CI: 15.6-25.4). In multivariate analysis, active disease at the time of SCT was significantly associated with increased NRM (*P*=0.01), while unrelated donors showed a trend toward a higher NRM (Table 3, Figure 2A). Thus, 2-year NRM was 18% (95% CI: 12.8-23.9) in CR1 patients and 29% (95% CI: 15.6-43) in patients with active disease who underwent transplantation (HR=2.38, 95%CI: 1.17-4.84, *P*=0.02). The presence of chronic GvHD was significantly associated with more NRM in multivariate analysis (HR=2.38, 95% CI: 1.04-5.49, *P*=0.04). In patients transplanted in CR1, the interval from CR1 to SCT was significantly associated with NRM in univariate analysis, being 7% (95% CI: 2.9-14.3) for patients transplanted within 98 days from CR1 and 24% (95% CI: 15.2-33.5) for patients transplanted more than 98 days from CR1. In multivariate analysis, a 9/10 unrelated donor was significantly associated with more NRM compared to a sibling donor, whereas NRM from a 10/10 unrelated donor SCT was comparable to a sibling donor (*P*=0.03 and *P*=0.42, respectively). Thus, 2-year NRM was 32% (95% CI: 12-53.8) when the SCT was performed with a 9/10 unrelated donor, 17% (95% CI: 9.7-25.3) when a sibling donor was used, and 16% (95% CI: 9.2-25.6) when the donor was a 10/10 unrelated donor. A longer interval from CR1 to SCT remained significantly associated with higher NRM in multivariate analysis (*P*=0.04) (Table 4).

Relapse incidence

The 2-year cumulative RI in the overall series was 35.4% (95% CI: 29.6-41.3). RI strongly correlated with disease status at the time of SCT, at 26.1% (95% CI: 19.9-32.6), 56.8% (95% CI: 37.1-72.3) and 61.9% (95% CI: 44.9-77) for patients transplanted in CR1, CR2 and not in remission at the time of SCT, respectively (*P*<0.001) (Figure 2B). In multivariate analysis, both CR2 and active disease were significantly associated with increased RI compared to patients transplanted in CR1 (*P*<0.001 and *P*<0.001, respectively) (Table 3). The presence of chronic GvHD was not associated with less relapse (HR=0.96, 95% CI: 0.48-19, *P*=0.9). Focusing on patients transplanted in CR1, a significant correlation between RI and the interval from diagnosis to CR1 (*P*=0.003) was demonstrated in univariate analysis, in line with the significant association between relapse and the number of induction courses to achieve CR1 (*P*<0.001). Thus, RI was 17.5% (95% CI: 10-26.9) when the interval from diagnosis to CR1 was less than 42 days, and 34.4% (95% CI: 24.1-44.9) when this interval was greater than 42 days; this difference was confirmed in multivariate analysis (HR: 2.32, 95% CI: 1.15-4.7, *P*=0.02). Being in molecular remission at the time of SCT was also significantly associated with less relapse in CR1 patients (17% *vs.* 44%, *P*=0.001). Five out of 24 patients with persistent molecular disease at the time of SCT received donor lymphocyte infusion (DLI) compared to 11 out of 80 patients with molecular remission (*P*=0.4). Increasing age (as a continuous variable), NPM1 status, type of donor, and conditioning intensity did not influence RI in multivariate analysis. TCD showed a trend toward less relapse in multivariate analysis (HR=0.53, 95% CI: 0.27-1.04, *P*=0.06). Molecular status at the time of SCT was not included in the multivariate analysis due to an excess of missing data (N=108).

Overall survival, leukemia-free survival and graft-*versus*-host/relapse-free survival

Among the 291 patients, the 2-year probability of OS was 46.7% (95% CI: 40.4-53.1). Disease status at SCT was the most powerful factor influencing survival, with a 2-year OS of 58.7% (95% CI: 51.2-66.1) in patients transplanted in CR1, 28.8% (95% CI: 12.3-45.4) in those transplanted in CR2, and only 9.5% (95% CI: 0.6-18.4) when transplantation was performed in active disease (*P*<0.001) (Figure 2C). In multivariate analysis, only disease status at the time of SCT (CR2 and active disease compared to CR1) was significantly associated with decreased OS

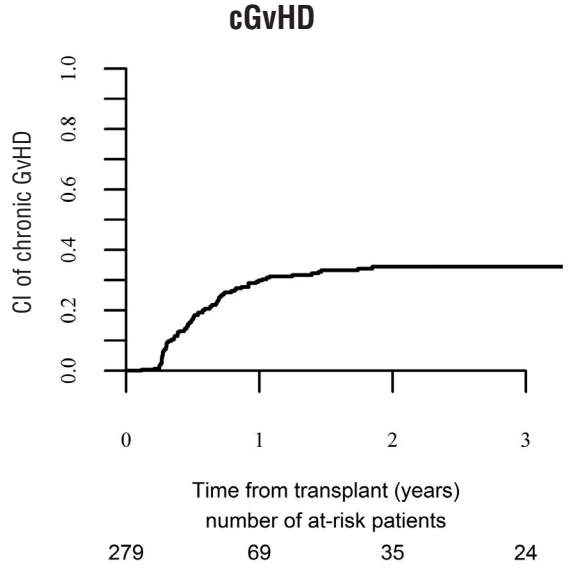

Figure 1. Cumulative incidence of chronic graft-*versus*-host disease (GvHD). The 2-year cumulative incidence of chronic GvHD was 34% (95% CI: 28.4-40.5) in the entire cohort (N=291).

(P<0.001; Table 3). Chronic GvHD was not associated with OS (HR=1.14, 95% CI: 0.74-1.79, P=0.57). In the cohort of CR1 patients, the 2-year probability of OS was 69.1% (95% CI: 58.9-79.4) in patients with an interval from diagnosis to CR1 of less than 42 days, and 54.9% (95% CI: 43.5-66.2) in patients with a longer interval to diagnosis of CR1 (P=0.06). We also found that a donor age of more than 47 years old was significantly associated with improved OS (P=0.02), however, donor's age was associated with donor type, being significantly older in HLA-identical siblings compared with unrelated donors (53 *vs.* 36 years old, P<0.001). When we compared the oldest sibling donors to the youngest unrelated donors according to median age in each group, we consistently found better OS with sibling donors, which confirms the stronger impact of donor type over donor's age. In multivariate analysis adjusted for patients' age, performance status, conditioning intensity, donor CMV status and *in vivo* TCD, older sibling donors were still associated with better OS (HR=0.38, P=0.008) compared to younger unrelated donors. Time from CR1 to SCT was significantly longer for the youngest unrelated donors (107 days, range: 9-198) compared to the oldest sibling donors (83 days, range: 13-186, P=0.04). The 2-year probability of OS was 62.7% (95% CI: 52.2-73.2) after SCT from a sibling donor, 57.7% (95% CI: 46.3-69.1) after SCT from a 10/10 unrelated donor and 42.2% (95% CI: 17.4-67) after SCT from a 9/10 unrelated donor, respectively, but those differences did not reach statistical significance across groups (P=0.27). Age (> or < 65 years old), *NPM1* status, molecular status at SCT, KPS, conditioning intensity, donor CMV positivity, and TCD were not correlated with OS in univariate analysis. In multivariate analysis, increasing patient's age as a continuous variable was significantly associated with better OS (HR=0.89, 95% CI: 0.8-0.99, P=0.03), and SCT from 9/10 unrelated donors compared

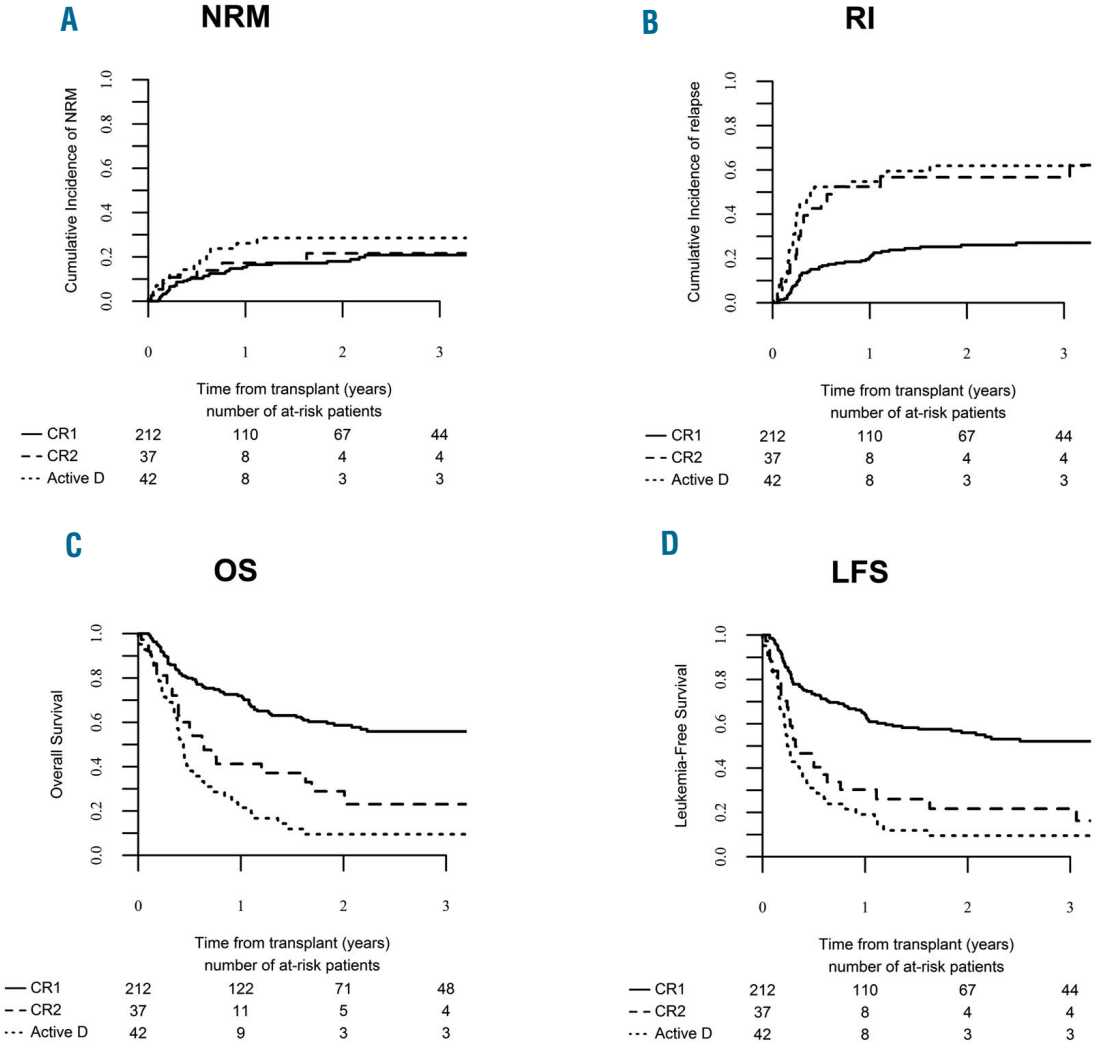

Figure 2. Non-relapse mortality (NRM), relapse incidence (RI), overall survival (OS) and leukemia-free survival (LFS) per disease status (first complete remission (CR1), second remission (CR2) and active disease (Active D)). (A) The 2-year cumulative incidence of NRM was 18% (95% CI: 12.8-23.9) in CR1 patients, 21.6% (95% CI: 8.9-37.9) in CR2 patients and 28.6% (95% CI: 15.6-43) in Active D patients. (B) The 2-year cumulative incidence of relapse was 26.1% (95% CI: 19.9-32.6) in CR1 patients, 56.8% (95% CI: 37.1-72.3) in CR2 patients and 61.9% (95% CI: 44.9-75) in Active D patients. (C) The 2-year probability of OS was 58.7% (95% CI: 51.2-66.1) in CR1 patients, 28.8% (95% CI: 12.3-45.4) and 9.5% (95% CI: 0.6-18.4) in Active D patients. (D) The 2-year probability of LFS was 55.9% (95% CI: 48.6-63.3) in CR1 patients, 21.6% (95% CI: 6.4-36.8) and 9.5% (95% CI: 0.6-18.4).

to sibling donors showed a trend toward worse OS (P=0.09) (Table 4).

The 2-year probability of LFS was 44.3% (95% CI: 38.1-50.5) for the whole patient cohort. Disease status had the strongest impact on LFS, with a 2-year LFS of 55.9% (95% CI: 48.6-63.3) in patients transplanted in CR1, 21.6% (95% CI: 6.4-36.8) if transplanted in CR2 and 9.5% (95% CI: 0.6-18.4) in patients not in CR at the time of SCT (P<0.001) (Figure 2D). In multivariate analysis, the significant influence of disease status at SCT was confirmed (P<0.001), and donor CMV positivity was also significantly associated with worse LFS (P=0.04) (Table 3). Chronic GvHD did not correlate with LFS (HR=1.51, 95% CI: 0.92-2.48, P=0.1). In the cohort of patients transplanted in CR1, an interval from diagnosis to CR1 of less than 42 days was significantly associated with better LFS (64.6% *vs.* 52.5%, P=0.03). On the contrary, other variables such as age (> or < 65 years old), *NPM1* status, TCD, donor CMV positivity or conditioning intensity did not show a prognostic impact on LFS. Similarly to OS, we observed a better LFS in SCT from donors aged over 47 years old in univariate (P=0.02) and multivariate analysis (P=0.01). The 2-year

Table 3. Multivariate analysis using a Cox proportional hazards model, N=291. Shown are variables with P<0.15 in univariate analysis. Non-relapse mortality, relapse incidence, overall survival and leukemia-free survival.

		P	HR	95% CI	
NRM	Age (per year)	0.57	0.97	0.89	1.07
	Status at SCT (CR1 as reference)				
	CR2	0.36	1.55	0.61	3.90
	Advanced	0.02	2.38	1.17	4.84
	Type of donor (MSD as reference)				
	10/10 UD	0.06	1.85	0.97	3.52
	9/10 UD	0.11	2.02	0.85	4.82
	Karnoksky > 90%	0,15	0.66	0.37	1.16
	RIC	0.39	0.75	0.38	1.47
	Donor CMV+	0.07	1.76	0.95	3.26
	In vivo TCD	0.90	1.04	0.56	1.92
RI	Age (per year)	0.23	0.96	0.89	1.03
	Status at SCT (CR1 as reference)				
	CR2	0.00001	4.59	2.37	8.87
	Advanced	<0.00001	4.23	2.42	7.39
	Type of donor (MSD as reference)				
	10/10 UD	0.81	0.94	0.56	1.57
	9/10 UD	0.68	0.86	0.41	1.78
	Karnoksky > 90%	0.72	1.10	0.67	1.79
	RIC	0.63	1.16	0.64	2.08
	Donor CMV+	0.21	1.37	0.84	2.25
	In vivo TCD	0.15	0.71	0.44	1.13
OS	Age (per year)	0.31	0.97	0.91	1.02
	Status at SCT (CR1 as reference)				
	CR2	0.0004	2.64	1.53	4.55
	Advanced	<0.00001	3.35	2.13	5.26
	Type of donor (MSD as reference)				
	10/10 UD	0.17	1.34	0.88	2.03
	9/10 UD	0.26	1.40	0.79	2.48
	Karnoksky > 90%	0.41	0.85	0.58	1.25
	RIC	0.53	1.16	0.72	1.87
	Donor CMV+	0.06	1.47	0.99	2.19
	In vivo TCD	0.43	0.85	0.58	1.26
LFS	Age (per year)	0.19	0.96	0.91	1.02
	Status at SCT (CR1 as reference)				
	CR2	0.00004	3.04	1.79	5.16
	Advanced	<0.00001	3.30	2.13	5.11
	Type of donor (MSD as reference)				
	10/10 UD	0.31	1.23	0.83	1.83
	9/10 UD	0.51	1.21	0.69	2.11
	Karnoksky > 90%	0.51	0.89	0.61	1.28
	RIC	0.87	0.97	0.62	1.50
	Donor CMV+	0.04	1.51	1.03	2.23
	In vivo TCD	0.28	0.82	0.56	1.18

N: number; NRM: non-relapse mortality; RI: relapse incidence; OS: overall survival; LFS: leukemia-free survival; HR: hazard ratio; CI: confidence interval; SCT: stem cell transplantation; CR1: first complete remission; CR2: second remission; UD: unrelated donor; MSD: matched sibling donor; CMV: cytomegalovirus; TCD: T-cell depletion; RIC: reduced-intensity conditioning.

probability of LFS was 62.7% (95% CI: 52.2-73.2) after SCT from a sibling donor, 57.7% (95% CI: 46.3-69.1) after SCT from a 10/10 unrelated donor, and 42.2% (95% CI: 17.4-67) after SCT from a 9/10 unrelated donor, respectively, however, as with OS, those differences did not reach significance (P=0.27). In multivariate analysis, increasing patient's age as a continuous variable and a shorter interval from diagnosis to CR1 were both significantly associated with better LFS (P=0.03 and P=0.05, respectively) (Table 4).

The 2-year probability of GRFS was 32.3% (95% CI: 26.3-38.3) in the study population. A worse GRFS was seen with more advanced disease; 41.7% (95% CI: 34.3-49.2) in patients transplanted in CR1, 18.1% (95% CI: 3.6-32.6) and 2.4% (95% CI: 0-7.2) in patients with CR2 and active disease at the time of SCT, respectively (P<0.001) (Figure 3). Multivariate analysis performed on GRFS within the entire cohort and the CR1 patients is available in the *Online Supplementary Material*.

We also focused on the two main conditioning regimens within CR1 patients, which were fludarabine and busulfan (N=95), followed by fludarabine and melphalan (N=30). We found no significant differences in terms of acute and chronic GvHD incidence, NRM, RI, OS and LFS between those two regimens in univariate analysis (*data not shown*).

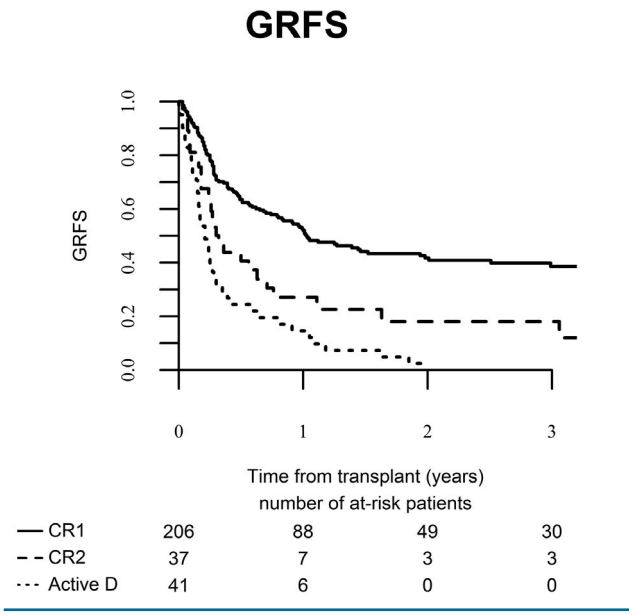

Figure 3. Graft-*versus*-host disease and relapse-free survival (GRFS) per disease status (first complete remission (CR1), second remission (CR2) and active disease (Active D)). The 2-year probability of GRFS was 41.7% (95% CI: 34.3-49.2) in CR1 patients, 18.1% (95% CI: 3.6-32.6) in CR2 patients and 2.4% (95% CI: 0-7.2) in Active D patients.

Discussion

SCT is becoming a routine standard of care consolidation strategy for younger patients with AML and *FLT3*-ITD.[3,8-11,23] Nonetheless, its potential benefit for older patients has not been specifically addressed, and there is currently no strong evidence which supports SCT for elderly patients with *FLT3*-ITD AML.[13,24] Against this background, our study demonstrated that in patients with an age equal to or over 60 years old, SCT performed in CR1 translates into a 2-year OS and LFS of 59% and 56%, respectively. A NRM and RI rate of 18% and 25%, respectively, are acceptable in this population. Interestingly, these results are only slightly inferior than those reported in younger patients, and suggest the relevance of graft-*versus*-leukemia (GvL) for disease control in this entity.[8,13,24] Moreover, increasing age was not associated with NRM and other outcomes within our population, probably reflecting a careful and adequate selection process in the elderly AML population submitted to SCT in CR1. On the contrary, we found very poor outcomes when SCT was performed beyond CR1, thus, the benefit of SCT in these situations remains questionable. The inferior results obtained in CR2 patients are in accordance with previous publications.[25,26] Based on our sizable dataset, we strongly recommend that SCT is offered as the best consolidation strategy for eligible patients in early disease phase with AML and *FLT3*-ITD.[27-29]

It is possible that we have to concede a selection bias in our study, howbeit this bias supports the need for a thorough evaluation of each older candidate prior to SCT. We did not find any difference in characteristics between the youngest and oldest patients from our population, such as time from diagnosis to CR1, conditioning regimen, hematopoietic cell transplant co-morbidity index (HCT-CI) or KPS. The superior OS and LFS observed among the oldest patients of our study may be explained by individual characteristics not reported in the registry. KPS and HCT-CI are well-described tools used to evaluate patients before SCT, and are reliable even in older patients.[15,17] In addition to HCT-CI, other tools have been described in the assessment of elderly patients undergoing anti-leukemic therapy, and found that chronologic age is definitively not a limiting factor.[16,30-32] This assessment included the functional, cognitive, biological, nutritional and medical evaluation of each patient, and helped us to discern the best candidate for intensive therapy or SCT.[33,34]

NPM1 mutation had no impact on any outcome parameter in this study. The favorable prognostic influence of *NPM1* has been demonstrated in patients of up to 65 years of age, although it is less pronounced or even lost in older subjects.[35,36] Several studies focused on younger patients have shown that *NPM1* mutation may influence OS and LFS in *FLT3*-ITD AML,[37-39] however, this impact is observed primarily in patients with a low allelic ratio of *FLT3*-ITD.[37,39,40] In *NPM1*-mutated AML, only patients harboring a high level of *FLT3*-ITD may benefit unequivocally from SCT.[41-44] Information regarding the *FLT3*-ITD allelic burden was not available in our study, and, given the lack of current standardization, it remains extremely difficult to analyze it in a multicenter registry setting.[45] Moreover, the concurrent mutation of DNMT3A, frequently found in combination with *FLT3*-ITD and *NPM1* mutation, may have a profound adverse prognostic impact, and the capacity for SCT to overcome this poor prognosis is currently unknown.[2,46-48] We also found that patients transplanted in molecular remission at the time of SCT had a better outcome after SCT, with a decreased relapse risk and a trend toward improved LFS and GRFS, a fact which has been recently addressed by Gaballa *et al.*[49] Nonetheless, the role of upfront SCT for patients who fail to achieve a molecular remission before SCT is unknown, and the benefit of donor lymphocyte infusion or other

Table 4. Multivariate analysis using a Cox proportional hazards model, N=212 (CR1 patients). Shown are variables with *P*<0.15 in univariate analysis. Non-relapse mortality, relapse incidence, overall survival and leukemia-free survival.

		P	HR	95% CI	
NRM	Age (per year)	0.15	0.88	0.75	1.05
	Type of donor (MSD as reference)				
	10/10 UD	0.42	1.46	0.58	3.68
	9/10 UD	0.03	3.58	1.15	11.13
	Kanofsky > 90%	0.10	0.52	0.23	1.14
	RIC	0.28	0.56	0.20	1.61
	Diagnosis to CR1 > 42 days	0.61	1.23	0.56	2.68
	CR1 to SCT > 98 days	0.04	2.50	1.06	5.91
	In vivo TCD	0.75	1.15	0.50	2.66
RI	Age (per year)	0.10	0.90	0.79	1.02
	Type of donor (MSD as reference)				
	10/10 UD	0.41	1.36	0.65	2.87
	9/10 UD	0.71	0.76	0.17	3.41
	Kanofsky > 90%	0.37	1.45	0.64	3.25
	RIC	0.77	1.18	0.40	3.48
	Diagnosis to CR1 > 42 days	0.02	2.32	1.15	4.70
	CR1 to SCT > 98 days	0.21	0.63	0.31	1.28
	In vivo TCD	0.06	0.53	0.27	1.04
OS	Age (per year)	0.03	0.89	0.80	0.99
	Type of donor (MSD as reference)				
	10/10 UD	0.29	1.39	0.76	2.54
	9/10 UD	0.10	2.14	0.88	5.23
	Kanofsky > 90%	0.52	0.83	0.47	1.47
	RIC	0.87	0.94	0.43	2.06
	Diagnosis to CR1 > 42 days	0.16	1.47	0.86	2.52
	CR1 to SCT > 98 days	0.71	1.11	0.64	1.93
	In vivo TCD	0.36	0.78	0.45	1.34
LFS	Age (per year)	0.03	0.89	0.80	0.99
	Type of donor (MSD as reference)				
	10/10 UD	0.29	1.36	0.77	2.42
	9/10 UD	0.13	1.9	0.82	4.40
	Kanofsky > 90%	0.73	0.91	0.52	1.57
	RIC	0.64	0.84	0.40	1.75
	Diagnosis to CR1 > 42 days	0.05	1.67	1.02	2.79
	CR1 to SCT > 98 days	0.59	1.15	0.69	1.93
	In vivo TCD	0.25	0.74	0.44	1.23

N: number; NRM: non-relapse mortality; RI: relapse incidence; OS: overall survival; LFS: leukemia-free survival; HR: hazard ratio; CI: confidence interval; CR1: first complete remission; UD: unrelated donor; MSD: matched sibling donor; RIC: reduced-intensity conditioning; TCD: T-cell depletion.

maintenance therapy in this setting should be specifically addressed in future studies.

A relevant issue concerning *FLT3*-ITD AML is the potential benefit of the use of *FLT3* inhibitors in combination with intensive chemotherapy in patients undergoing SCT. In this regard, the addition of midostaurin to chemotherapy in newly diagnosed *FLT3*-ITD AML has been showed to significantly improve survival, even in patients undergoing SCT in CR1, suggesting that a deeper anti-leukemic response before SCT can translate into an improved outcome after transplant.[50] Since information on the use of *FLT3* inhibitors pre- and post-transplant was not available in this registry study, we were unable to specifically analyze their effects. The prevention of relapse after SCT[8,13] with post-transplant maintenance therapy based on *FLT3* inhibitors is an area of current preferential interest, and is being investigated *via* ongoing clinical trials using agents such as sorafenib, midostaurin or gilteritinib. Small retrospective studies on maintenance with sorafenib have resulted in reduced RI and improved survival without increased toxicity.[51-54] Nevertheless, SCT remains the best consolidation therapy offered to date, and the use of FLT3 inhibitors may only increase the proportion of patients, including frailer subjects, who might benefit from SCT.

Herein, transplantation from 9/10 unrelated donors was associated with significant higher NRM and a trend toward inferior OS and LFS compared to sibling donors and 10/10 unrelated donors, as previously reported.[55,56] However, an unrelated donor may be preferable due to the fact that older patients have older sibling donors, and donor age has been associated with decreased survival due to an excess of acute and chronic GvHD.[57] Of note, improved survival has been observed with the use of younger unrelated donors compared to older sibling donors in an EBMT retrospective study,[58] while another large study from the Center for International Blood and Marrow Transplant Research (CIBMTR) reported no difference in terms of outcomes between younger matched unrelated donors and older sibling donors.[59] Among our

CR1 patients, we found that older donor age (>47 years old) was associated with more chronic GvHD, but better OS and LFS, and had no effect on RI. However, the age of the donor was strongly associated with the type of donor. The effect of donor type on outcomes was more potent than that of donor age, and our observations favor the use of a sibling donor, if eligible for stem cell donation. If a sibling donor is not available, a 10/10 fully matched unrelated donor is a suitable option, but caution must be applied with the use of a 9/10 unrelated donor. Nevertheless, we found a shorter interval from CR1 to SCT with sibling donors compared to older donors. We suggest an early donor search in order to further improve the results obtained with unrelated donors. TCD was significantly associated with less chronic GvHD and less extensive chronic GvHD, with no effect on OS and LFS. We did not find a beneficial effect of chronic GvHD on RI and LFS to support the existence of a GvL effect in our population.

In conclusion, SCT emerges as a recommended consolidation strategy for fit patients aged 60 or over with AML and *FLT3*-ITD in CR1. Based on our study, and in view of the inferior results observed when SCT is performed in CR2 and beyond, we do not recommend postponing SCT until relapse. However, the few patients over 70 years of age included herein preclude firm recommendations for older patients. Sibling donors or fully matched unrelated donors remain the best donor choice in this older population.

References

1. Cancer Genome Atlas Research N, Ley TJ, Miller C, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368(22):2059-2074.
2. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221.
3. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008;358(18):1909-1918.
4. Kottaridis PD, Gale RE, Frew ME, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001;98(6):1752-1759.
5. Singh H, Asali S, Werner LL, et al. Outcome of older adults with cytogenetically normal AML (CN-AML) and FLT3 mutations. Leuk Res. 2011;35(12):1611-1615.
6. Whitman SP, Maharry K, Radmacher MD, et al. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. 2010;116(18):3622-3626.
7. Gale RE, Hills R, Kottaridis PD, et al. No evidence that FLT3 status should be considered as an indicator for transplantation in acute myeloid leukemia (AML): an analysis of 1135 patients, excluding acute promyelocytic leukemia, from the UK MRC AML10 and 12 trials. Blood. 2005; 106(10):3658-3665.
8. Brunet S, Labopin M, Esteve J, et al. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. J Clin Oncol. 2012; 30(7):735-741.
9. DeZern AE, Sung A, Kim S, et al. Role of allogeneic transplantation for FLT3/ITD acute myeloid leukemia: outcomes from 133 consecutive newly diagnosed patients from a single institution. Biol Blood Marrow Transplant. 2011;17(9):1404-1409.
10. Lin PH, Lin CC, Yang HI, et al. Prognostic impact of allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia patients with internal tandem duplication of FLT3. Leuk Res. 2013; 37(3):287-292.
11. Meshinchi S, Arceci RJ, Sanders JE, et al. Role of allogeneic stem cell transplantation in FLT3/ITD-positive AML. Blood. 2006; 108(1):400; author reply 400-1.
12. Laboure G, Dulucq S, Labopin M, et al. Potent graft-versus-leukemia effect after reduced-intensity allogeneic SCT for intermediate-risk AML with FLT3-ITD or wild-type NPM1 and CEBPA without FLT3-ITD. Biol Blood Marrow Transplant. 2012; 18(12):1845-1850.
13. Schmid C, Labopin M, Socie G, et al. Outcome of patients with distinct molecular genotypes and cytogenetically normal AML after allogeneic transplantation. Blood. 2015;126(17):2062-2069.
14. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363(22):2091-2101.
15. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. JAMA. 2011;306(17):1874-1883.
16. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010;28(3):405-411.
17. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. J Clin Oncol. 2014;32(29):3249-3256.
18. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood. 2013;121(21):4287-4294.
19. Dohner 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(4):424-447.
20. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-474.
21. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15(12):1628-1633.
22. Schmid C, Schleuning M, Ledderose G, et al. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. J Clin Oncol. 2005;23(24):5675-5687.
23. Berman E, Maloy M, Devlin S, et al. Stem cell transplantation in adults with acute myelogenous leukemia, normal cytogenetics, and the FLT3-ITD mutation. Leuk Res. 2016;40:33-37.
24. Oran B, Cortes J, Beitinjaneh A, et al. Allogeneic transplantation in first remission improves outcomes irrespective of FLT3-ITD allelic ratio in FLT3-ITD-positive acute myelogenous leukemia. Biol Blood Marrow Transplant. 2016;22(7):1218-1226.
25. Burnett AK, Goldstone A, Hills RK, et al. Curability of patients with acute myeloid leukemia who did not undergo transplantation in first remission. J Clin Oncol. 2013;31(10):1293-1301.
26. Forman SJ, Rowe JM. The myth of the second remission of acute leukemia in the adult. Blood. 2013;121(7):1077-1082.
27. Michelis FV, Messner HA, Atenafu EG, et al. Benefit of allogeneic transplantation in patients age >/= 60 years with acute myeloid leukemia is limited to those in first complete remission at time of transplant. Biol Blood Marrow Transplant. 2014;20(4):474-479.
28. Walter RB, Sandmaier BM, Storer BE, et al. Number of courses of induction therapy independently predicts outcome after allogeneic transplantation for acute myeloid leukemia in first morphological remission. Biol Blood Marrow Transplant. 2015; 21(2):373-378.
29. Deol A, Sengsayadeth S, Ahn KW, et al. Does FLT3 mutation impact survival after hematopoietic stem cell transplantation for acute myeloid leukemia? A Center for International Blood and Marrow Transplant Research (CIBMTR) analysis. Cancer. 2016;122(19):3005-3014.
30. Brunner AM, Kim HT, Coughlin E, et al.

Outcomes in patients age 70 or older undergoing allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Biol Blood Marrow Transplant. 2013;19(9):1374-1380.
31. Federmann B, Faul C, Meisner C, et al. Influence of age on outcome after allogeneic hematopoietic cell transplantation: a single center study in patients aged 60. Bone Marrow Transplant. 2015;50(3):427-431.
32. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010; 28(3):405-411.
33. Muffly LS, Boulukos M, Swanson K, et al. Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. Biol Blood Marrow Transplant. 2013;19(3):429-434.
34. Muffly LS, Kocherginsky M, Stock W, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. Haematologica. 2014;99(8):1373-1379.
35. Lazenby M, Gilkes AF, Marrin C, et al. The prognostic relevance of flt3 and npm1 mutations on older patients treated intensively or non-intensively: a study of 1312 patients in the UK NCRI AML16 trial. Leukemia. 2014;28(10):1953-1959.
36. Ostronoff F, Othus M, Lazenby M, et al. Prognostic significance of NPM1 mutations in the absence of FLT3-internal tandem duplication in older patients with acute myeloid leukemia: a SWOG and UK National Cancer Research Institute/Medical Research Council report. J Clin Oncol. 2015;33(10):1157-1164.
37. de Jonge HJ, Valk PJ, de Bont ES, et al. Prognostic impact of white blood cell count in intermediate risk acute myeloid leukemia: relevance of mutated NPM1 and FLT3-ITD. Haematologica. 2011;96(9):1310-1317.
38. Gale RE, Green C, Allen C, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008;111(5):2776-2784.
39. Schnittger S, Bacher U, Kern W, et al. Prognostic impact of FLT3-ITD load in NPM1 mutated acute myeloid leukemia. Leukemia. 2011;25(8):1297-1304.
40. Pratcorona M, Brunet S, Nomdedeu J, et al. Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. Blood. 2013; 121(14):2734-2738.
41. Ho AD, Schetelig J, Bochtler T, et al. Allogeneic stem cell transplantation improves survival in patients with acute myeloid leukemia characterized by a high allelic ratio of mutant FLT3-ITD. Biol Blood Marrow Transplant. 2016;22(3):462-469.
42. Schlenk RF, Kayser S, Bullinger L, et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. Blood. 2014;124(23):3441-3449.
43. Versluis J, In 't Hout FE, Devillier R, et al. Comparative value of post-remission treatment in cytogenetically normal AML subclassified by NPM1 and FLT3-ITD allelic ratio. Leukemia. 2017;31(1):26-33.
44. Linch DC, Hills RK, Burnett AK,et al. Impact of FLT3(ITD) mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia. Blood. 2014;124(2):273-276.
45. Pratz KW, Levis M. How I treat FLT3-mutated AML. Blood. 2017;129(5):565-571.
46. Ahn JS, Kim HJ, Kim YK, et al. DNMT3A R882 mutation with FLT3-ITD positivity is an extremely poor prognostic factor in patients with normal-karyotype acute myeloid leukemia after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2016;22(1):61-70.
47. Garg M, Nagata Y, Kanojia D, et al. Profiling of somatic mutations in acute myeloid leukemia with FLT3-ITD at diagnosis and relapse. Blood. 2015; 126(22):2491-2501.
48. Metzeler KH, Herold T, Rothenberg-Thurley M, et al. Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood. 2016;128(5):686-698.
49. Gaballa S, Saliba R, Oran B, et al. Relapse risk and survival in patients with FLT3 mutated acute myeloid leukemia undergoing stem cell transplantation. Am J Hematol. 2017;92(4):331-337.
50. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
51. Antar A, Kharfan-Dabaja MA, Mahfouz R, et al. Sorafenib Maintenance Appears Safe and Improves Clinical Outcomes in FLT3-ITD Acute Myeloid Leukemia After Allogeneic Hematopoietic Cell Transplantation. Clin Lymphoma Myeloma Leuk. 2015;15(5):298-302.
52. Brunner AM, Li S, Fathi AT, et al. Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT3-ITD acute myeloid leukaemia in first complete remission. Br J Haematol. 2016;175(3):496-504.
53. Chen YB, Li S, Lane AA, et al. Phase I trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. Biol Blood Marrow Transplant. 2014; 20(12):2042-2048.
54. Metzelder SK, Schroeder T, Finck A, et al. High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. Leukemia. 2012; 26(11):2353-2359.
55. Verneris MR, Lee SJ, Ahn KW, et al. HLA mismatch is associated with worse outcomes after unrelated donor reduced-intensity conditioning hematopoietic cell transplantation: an analysis from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant. 2015;21(10):1783-1789.
56. Piemontese S, Ciceri F, Labopin M, et al. A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. J Hematol Oncol. 2017;10(1):24.
57. Kollman C, Howe CW, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood. 2001;98(7):2043-2051.
58. Kroger N, Zabelina T, de Wreede L, et al. Allogeneic stem cell transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. Leukemia. 2013;27(3):604-609.
59. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? Blood. 2013; 121(13):2567-2573