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Autologous

Postremission Consolidation by Autologous Hematopoietic Cell Transplantation (HCT) for Acute Myeloid Leukemia in First Complete Remission (CR) and Negative Implications for Subsequent Allogeneic HCT in Second CR: A Study by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

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A B S T R A C T

After autologous hematopoietic cell transplantation (HCT) in the first complete remission (CR1), patients with acute myeloid leukemia (AML) may relapse and undergo allogeneic HCT in the second complete remission (CR2). The aim of this study was to analyze the outcome of allogeneic HCT performed in CR2 comparing patients with prior consolidation by autologous HCT versus patients with chemotherapy consolidation. Included were 2619 adults with allogeneic HCT in CR2 from 2000 to 2017 with (n = 417) or without (n = 2202) prior autologous HCT. Patient groups were not entirely comparable; patients with prior autologous HCT were younger, had less often a favorable cytogenetic profile, had more commonly donors other than matched siblings, and more often received reduced-intensity conditioning. In multivariate analysis, nonrelapse mortality risks in patients with prior autologous HCT were 1.34 (1.07 to 1.67; *P* = .01) after adjustment for age, cytogenetic risk, transplant year, donor, conditioning intensity, sex matching, interval diagnosis-relapse, and relapse-allogeneic HCT as compared with chemotherapy consolidation. Similarly, risks of events in leukemia-free survival and graft-versus-host disease, relapse-free survival were higher with prior autologous HCT, 1.17 (1.01 to 1.35), *P* = .03 and 1.18 (1.03 to 1.35), *P* = .02, respectively. Risk of death was also higher, 1.13 (0.97 to 1.32), *P* = .1, but this was not significant. Postremission consolidation with autologous HCT for AML in CR1 increases toxicity of subsequent allogeneic HCT in CR2.
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INTRODUCTION

During the past decades, autologous hematopoietic cell transplantation (HCT) has been widely used as consolidation treatment in patients with acute myeloid leukemia (AML) in

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first complete remission (CR1) or second complete remission (CR2) [1-11]. Over time, donors for allogeneic stem cell transplantation have become available, and allogeneic HCT appears to have in part replaced autologous HCT.

Autologous HCT was shown to reduce relapse rates by approximately 10% and increase leukemia-free survival (LFS) but not overall survival in a randomized clinical study [1]. Consolidation by autologous HCT is used more commonly in patients with low- and intermediate-risk AML, whereas for high-risk AML, allogeneic HCT is more commonly recommended. Up to half of patients receiving consolidation by autologous HCT in CR1 will relapse and will be candidates for allogeneic HCT in CR2 [1]. Although observational registry studies will not be able to answer whether a strategy of early allogeneic HCT is better than consolidation by chemotherapy or autologous HCT and allogeneic HCT in case of relapse, the toxicity of allogeneic HCT in CR2 in patients having received consolidation treatment by autologous HCT or by chemotherapy can be quantified and compared.

This study compares mortality after allogeneic HCT in CR2 in patients with AML who have received consolidation treatment in CR1 by autologous HCT versus those who have received consolidation by chemotherapy only. A difference in mortality may indicate added burden of toxicity by autologous HCT consolidation in case later allogeneic HCT is required to treat relapsed disease.

PATIENTS AND METHODS

This is an observational study including adult patients (≥18 years) with de novo AML (non-acute promyleocytic leukemia) registered with the European Society for Blood and Marrow Transplantation (EBMT) receiving an allogeneic HCT in CR2 between 2000 and 2017 and who had received either chemotherapy consolidation (n = 2202) or consolidation by autologous HCT (n = 417) in CR1. Included were patients in whom the date of relapse was reported and whose donor was a matched sibling, an unrelated donor, or a haploidentical donor.

The EBMT is a nonprofit scientific society representing more than 600 transplant centers, mostly located in Europe, that are required to report all consecutive stem cell transplantations and follow-up data once a year. Data are entered, managed, and maintained in a central database with Internet access; each EBMT center is represented in this database. Audits are routinely performed to determine the accuracy of the data. Patients or their legal guardians provide informed consent authorizing the use of their personal information for research purposes according to the Declaration of Helsinki. The Review Board of the EBMT approved this study.

ENDPOINTS

The main outcome of this study was nonrelapse mortality (NRM) of allogeneic HCT in CR2 comparing patients with prior autologous HCT to patients with chemotherapy consolidation. NRM was defined as death without evidence of relapse or progression. CR was understood as complete hematologic remission, and this was defined as less than 5% bone marrow blasts. Relapse was defined as the presence of 5% or more bone marrow blasts after remission was obtained.

Secondary outcomes were overall survival (OS), defined as time from allogeneic HCT in CR2 to death from any cause. LFS was defined as time from allogeneic HCT in CR2 to relapse or progression or death from any cause. Acute graft-versus-host disease (GVHD) was graded according to the modified Seattle-Glucksberg criteria [12] and chronic GVHD according to the revised Seattle criteria [13]. GVHD-free, relapse-free survival (GRFS) was defined using the EBMT definition for registry-based analyses where the time to first event among the following is recorded: severe grade III or IV acute GVHD, severe chronic GVHD, relapse, and death [14].

DEFINITIONS

Conditioning regimen was defined myeloablative conditioning (MAC) when containing total body irradiation (TBI) 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 reduced-intensity conditioning (RIC) [15]. Cytogenetic abnormalities were classified according to medical research council UK criteria [16].

STATISTICS

Groups were compared using the Mann-Whitney *U* test for continuous variables and chi-squared test for categorical variables. Cumulative incidence was used to estimate the endpoints of NRM and relapse incidence to accommodate competing risks [17,18]. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier method [19]. Univariate analyses were done using the Gray test for cumulative incidence functions and the log-rank test for OS, GRFS, and LFS. Continuous variables were entered as continuous covariates in multivariate analyses. Cox proportional hazards models were run to adjust for differences among groups [20,21], entering all variables differing significantly between the 2 groups. All variables differing significantly between the 2 groups or factors known to influence outcomes were included in the Cox model: patient age, year of transplant, time from diagnosis to relapse, and time from relapse to allograft were included as continuous variables. Other variables were cytogenetic risk group (favorable, intermediate, adverse, or NA), donor type, conditioning intensity, sex matching, Karnofsky performance score, and patient cytomegalovirus serology. Probabilities of the respective survival times are reported at 2 years after allogeneic HCT. To test for a center effect, we introduced a random effect or frailty for each center into the model [22,23]. Results were expressed as the hazard ratio with the 95% confidence interval%. All tests were 2-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 24.0 (SPSS, Inc, Chicago, IL) and R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

This study included 2619 adults with de novo AML who received their first allogeneic HCT in CR2 from 2000 to 2017. In total, 417 patients had undergone autologous HCT as part of the consolidation treatment in CR1 and had subsequently relapsed, and 2202 patients had undergone consolidation treatment by chemotherapy only. Patient, disease, and treatment characteristics are shown in Table 1. Patients with prior autologous HCT differed from patients with chemotherapy consolidation in many ways. They were younger by 2.7 years, had undergone transplantation earlier (median 2009 as compared with 2010), less often had a favorable cytogenetic profile, more commonly underwent transplantation with alternative donors other than matched siblings, and more often had RIC as compared with MAC conditioning. Patients with prior autologous HCT had an interval to relapse that was shorter by a median of 41 days from diagnosis of AML. Time from CR2 to allogeneic HCT was comparable in both groups.

Conditioning for prior autologous HCT was by TBI in 50, by busulfan in combination with cyclophosphamide in 168, with melphalan in 56, with other drugs in 34, and by drug combinations not containing busulfan in 23. The type of conditioning for prior autologous HCT was unknown in 86; these had not been reported as transplants to the EBMT.

Table 1
Patient Disease and Transplant Characteristics

Characteristic	Chemotherapy Consolidation	Autologous HCT Consolidation	*P* Value
Number	2202	417	
Age (IQR), yr	48.2 (36.9-58.4)	45.5 (36-55.5)	.003
Year of transplant	2010 (2006-2014)	2009 (2005-2013)	.002
Time to first relapse, d	406 (281-630)	365 (222-695)	.03
Time relapse to allogeneic HCT, d	130 (15-361)	128 (29-363)	NS
Genetic risk category, n (%)			.001
Favorable	569 (29.0%)	55 (18.8%)	
Intermediate	1244 (63.5%)	216 (73.7%)	
Unfavorable	146 (7.5%)	22 (7.5%)	
Karnofsky performance score, n (%)			.92
<80	101 (5.1%)	20 (5.2%)	
≥80	1888 (94.9%)	365 (94.8%)	
Patient CMV serology, n (%)			.38
Negative	785 (36.3%)	123 (33.9%)	
Positive	1380 (63.7%)	240 (66.1%)	
Donor, n (%)			.0001
Matched sibling	763 (34.7%)	77 (18.5%)	
Unrelated	1291 (58.6%)	301 (72.2%)	
Haploidentical	148 (6.7%)	39 (9.4%)	
Donor recipient sex mismatch, n (%)			.22
Female into male	401 (18.3%)	65 (15.7%)	
Other combinations	1792 (81.7%)	348 (84.3%)	
Conditioning, n (%)			.0001
Myeloablative	1227 (55.8%)	190 (46.1%)	
Reduced intensity	973 (44.2%)	222 (53.9%)	
In vivo T cell depletion, n (%)			.08
Yes	1252 (57.3%)	230 (62.2%)	
No	934 (42.7%)	140 (37.8%)	
In vitro T cell depletion, n (%)	79 (3.6%)	23 (5.5%)	.06
Stem cell source, n (%)			.11
BM	451 (20.5%)	100 (24.0%)	
PB	1751 (79.5%)	317 (76.0%)	

IQR indicates interquartile range; NS, not significant; CMV, cytomegalovirus; BM, bone marrow; PB, peripheral blood.

Univariate outcomes are shown in Table 2 and in Figures 1 (NRM) and 2 (LFS). In univariate analysis, NRM was higher and LFS lower by approximately 4% in patients with prior autologous HCT consolidation as compared with chemotherapy consolidation. Given the important differences among groups, multivariate analysis adjusting for these differences, including patient age, cytogenetic risk, year of transplant, donor type, conditioning intensity, sex matching, the time interval from diagnosis to relapse, and the time interval from relapse to allogeneic HCT into the model, is more reliable.

Relative risks of NRM were 1.34 (1.07 to 1.67; *P* = .01) in patients with prior autologous HCT versus chemotherapy consolidation. Similarly, LFS risks were 1.17 (1.01 to 1.35; *P* = .03), GRFS risks were 1.18 (1.03 to 1.35, *P* = .02), and OS was 1.13 (0.974 to 1.32; *P* = .1) comparing the groups with prior autologous HCT to patients with chemotherapy consolidation. A subgroup of patients with prior autologous HCT had a particularly poor outcome; these patients had received conditioning by TBI for autologous HCT (n = 50), contributing to higher mortality of subsequent allogeneic HCT, which had been reported in a

Table 2
Univariate and Multivariate Outcomes

Characteristic	Chemotherapy Consolidation	Autologous HCT Consolidation	*P Value*	MVA*	*P Value*
NRM (2 yr)	21.3 (19.6-23.1)	25.2 (21-29.6)	.008	1.32 (1.03-1.69)	.03
Relapse (2 yr)	28.1 (26.1-30)	28.6 (24.1-33.2)	NS	1.07 (0.85-1.34)	.58
OS (2 yr)	58.1 (55.9-60.2)	55.2 (50.2-60.2)	.02	1.19 (1.01-1.41)	.04
LFS (2 yr)	50.6 (48.4-52.8)	46.2 (41.2-51.2)	.004	1.20 (1.02-1.41)	.03
GRFS (2 yr)	39.7 (37.5-41.8)	35.7 (30.8-40.5)	.02	1.18 (1.01-1.38)	.03
Acute GVHD II-IV (100 d)	25.6 (23.8-27.5)	23.7 (19.6-28)	.33	0.87 (0.66-1.13)	.29
Chronic GVHD (2 y)	40.2 (37.9-42.4)	37.5 (32-43)	.27	0.93 (0.73-1.19)	.56

MVA indicates multivariate analysis, NRM probability of NRM in the MVA this is hazard rate.
* Baseline is chemotherapy consolidation with a relative risk of event of 1.00.

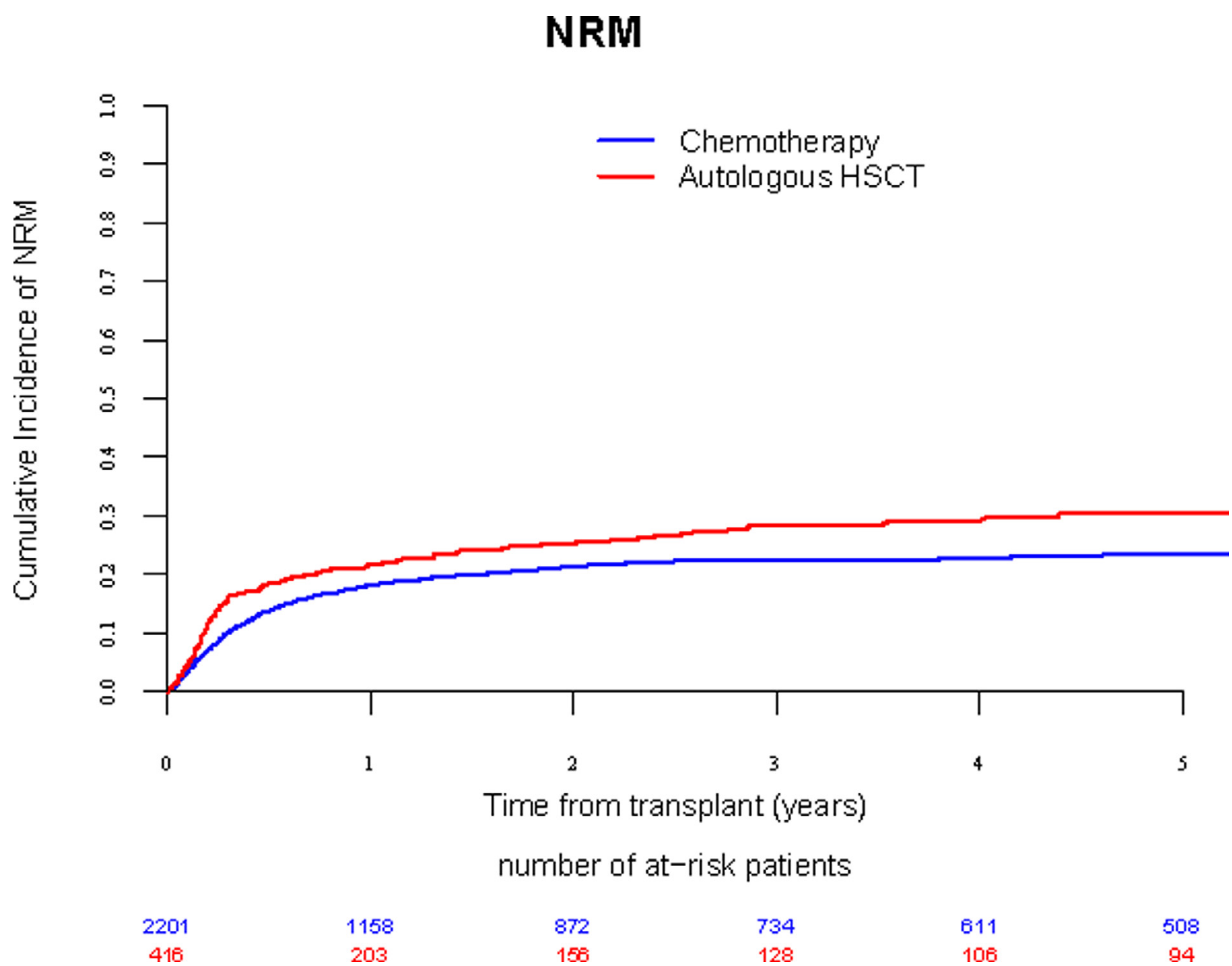

Figure 1. Univariate NRM incidence for patients with prior autologous HCT consolidation versus chemotherapy consolidation.

previous study by our group [10]. Relative risk of NRM was 1.32 (1.03 to 1.69) comparing patients with prior autologous HCT consolidation to patients without. When analyzing patients with autologous HCT conditioning without TBI separately from patients with TBI, the risk of NRM of the non-TBI patients was 1.21 (0.957 to 1.54) as compared with patients without autologous HCT. Conversely, NRM risks of allogeneic HCT were highest in the patients with TBI conditioning for autologous HCT (relative risk: 2.7 [1.67 to 4.37]). Causes of death after allogeneic HCT in CR2 in both groups were dominated by relapsed disease in 39.1% and 46.7%, GVHD in 16.4% and 19.9%, and infectious disease in 26.8% and 19.4% when comparing patients with autologous HCT consolidation to chemotherapy consolidation in CR1. Sinusoidal obstruction syndrome of the liver was the cause of death in 2.7% versus 1.9%, interstitial pneumonitis in 4.1% versus 2.7%, cardiac toxicity in 0.9% versus 0.7%, and secondary malignancy in 3.2% versus 1.7% of patients, respectively. The *P* value of comparing cause of death was .28.

DISCUSSION

Use of autologous HCT for AML is not well standardized. Some groups advocate this strategy as appropriate consolidation treatment in patients with genetically low- or intermediate-risk AML. Use, particularly in CR1, shows a steep increase over the 1990s, with a rapid drop after 2000, as reported to the EBMT activity survey. Authors interpret the data as showing a probable switch to allogeneic HCT consolidation at the time when HLA high-resolution typing became available and large numbers of unrelated donors were accessible for HCT, rather than the result of comparative studies, of which only relatively few have been published.

The best evidence for autologous HCT in CR1 comes from a randomized clinical trial showing a reduced relapse rate by approximately 10% with improved LFS but no significant difference in OS [1] published in 2011. This study had not found an interaction between relapse risk reduction by autologous HCT and genetic risk categories. Patients in CR1, even if in genetic low- and intermediate-risk categories, would have a risk of relapse of 40% to 50% even after consolidation by autologous HCT [1]. Relapsing patients would most commonly undergo reinduction chemotherapy following consolidation in CR2 by allogeneic HCT.

Previous studies from the acute leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) had compared the outcome of patients with acute leukemia with a relapse after autologous HCT treated with chemotherapy, a second autologous HCT, or an allogeneic HCT [6,7]. In these studies with patients treated before 2000, outcome was not significantly different after a second autograft or an allogeneic HCT with OS of 42% ± 6% and 32% ± 5%, respectively. Young age and interval from first autograft to the second transplant >8 months and the absence of prior TBI had a more favorable outcome. Outcome of patients treated without a second transplant was very poor. A study published in 2013 with 302 patients undergoing an unrelated allogeneic

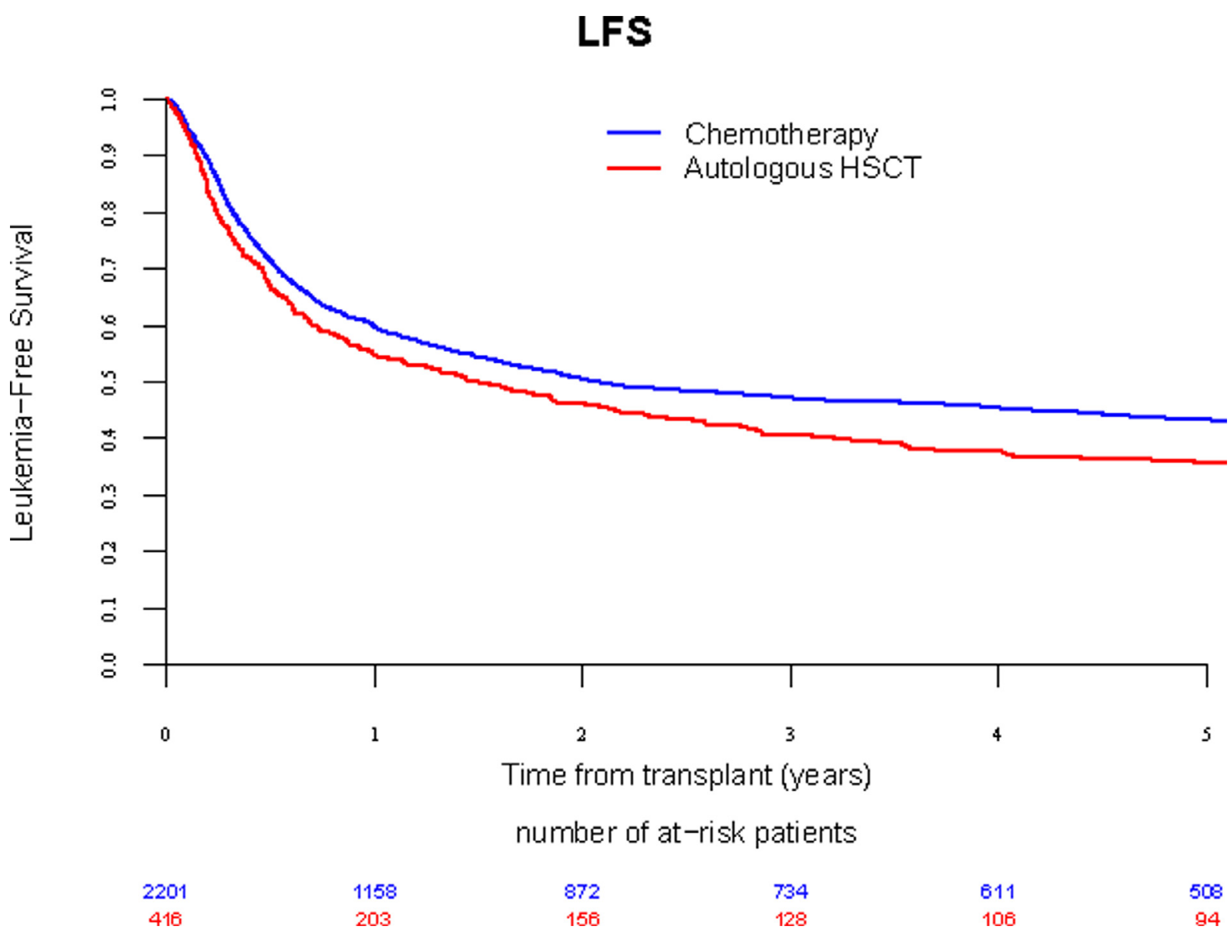

Figure 2. Univariate LFS probabilities for patients with prior autologous HCT consolidation versus chemotherapy consolidation.

HCT for relapse after autologous HCT with either MAC or RIC showed a LFS of 20% at 5 years. Results were better in patients with a longer interval to second HCT, a high Karnofsky performance score, and RIC [8]. These studies, as well as a study recently published by the ALWP of the EBMT [10], looked at the outcome of allogeneic HCT following relapse after autologous HCT and reported that patients with less aggressive disease and in a better state of health fared better. However, these studies did not address whether prior autologous HCT affected the toxicity of subsequent allogeneic HCT.

Here we provide evidence that toxicity measured as NRM is increased after allogeneic HCT in CR2 if consolidation in CR1 had been by autologous HCT rather than chemotherapy alone. However, differences are small (ie, approximately 4% by univariate analysis), and it is not clear whether this difference is driven by cumulative toxicity of higher doses of chemotherapy or by other factors. The groups of patients with prior autologous HCT and chemotherapy consolidation differed in many aspects, and groups were heterogeneous. In particular, patients with prior autologous HCT had more commonly RIC for allogeneic HCT in CR2, despite them being younger as compared with the chemotherapy consolidation group. As this is an observational study, we do not have control over treatment choices and assume that RIC regimens were chosen more commonly to avoid toxicity considered to be higher, given prior autologous HCT conditioning. Patients with prior autologous HCT had more often intermediate-risk cytogenetics as compared with the chemotherapy consolidation group, pointing toward a (desired) selection bias. There were, however, no differences in relapse rates. We carefully adjusted for these differences by multivariate analysis, particularly for conditioning intensity, but other factors not measured or not appreciated sufficiently may have an impact. For instance, we lack information on the number of chemotherapy cycles to achieve CR1 as well as the number of cycles to achieve CR2. In addition, there are data missing on the conditioning regimen of autologous HCT in a proportion of these patients. Patients with conditioning for autologous HCT by TBI fared particularly poorly, but patients without TBI conditioning had higher NRM risks, although this was only of borderline significance. Last, this study is obviously agnostic to the benefit of autologous HCT in CR1 (ie, we only analyzed patients who experienced a relapse and achieved CR2). We also do not know about patients who did not achieve a CR2 or patients who could not undergo an allogeneic HCT in CR2 because of lack of donor or comorbid conditions. Despite these limitations, this study shows that patients receiving an allograft in CR2 may be at a slightly higher risk of nonrelapse mortality after having received a consolidation treatment by autologous HCT as compared with chemotherapy consolidation.

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