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Comparison of Intensive Chemotherapy and Hypomethylating Agents before Allogeneic Stem Cell Transplantation for Advanced Myelodysplastic Syndromes: A Study of the Myelodysplastic Syndrome Subcommittee of the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplant Research

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A B S T R A C T

The European Society for Blood and Marrow Transplant Research data set was used to retrospectively analyze the outcomes of hypomethylating therapy (HMA) compared with those of conventional chemotherapy (CC) before hematopoietic stem cell transplantation (HSCT) in 209 patients with advanced myelodysplastic syndromes. Median follow-up was 22.1 months and the median age of the group was 57.6 years with 37% of the

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population older than > 60 years. The majority of patients (59%) received reduced-intensity conditioning and 34% and 27% had intermediate-2 and high international prognostic scoring system (IPSS) scores. At time of HSCT, 32% of patients did not achieve complete remission (CR) and 13% had primary refractory disease. On univariate analysis, outcomes at 3 years were not significantly different between HMA and CC for overall survival (OS), relapse-free survival (RFS), cumulative incidence of relapse (CIR), and nonrelapse mortality (NRM): OS (42% versus 35%), RFS (29% versus 31%), CIR (45% versus 40%), and NRM (26% versus 28%). Comparing characteristics of the groups, there were more patients < 55 years old, more patients in CR (68% versus 32%), and fewer patients with primary refractory disease in the CC group than in the HMA group (10% versus 19%, $P < .001$). Patients with primary refractory disease had worse outcomes than those in CR with regard to OS (hazard ratio [HR], 2.42; 95% confidence interval [CI], 1.41 to 4.13; $P = .001$), RFS (HR, 2.27; 95% CI, 1.37 to 3.76; $P = .001$), and NRM (HR, 2.49; 95% CI, 1.18 to 5.26; $P = .016$). In addition, an adverse effect of IPSS-R cytogenetic risk group was evident for RFS. In summary, outcomes after HSCT are similar for patients receiving HMA compared with those receiving CC, despite the higher proportion of patients with primary refractory disease in the HMA group.

INTRODUCTION

Myelodysplastic syndromes (MDS) are potentially life-threatening clonal hematological disorders for which hematopoietic stem cell transplantation (HSCT) is the only curative therapy. The advent of reduced-intensity protocols has expanded the applicability of this procedure to those of advanced age and those who have comorbidities. This is particularly relevant given the older median age of the majority of the population diagnosed with MDS. Current data suggest that transplantation outcomes are influenced by a number of factors, with pretransplantation blast percentage, cytogenetic risk group, and remission status considered of particular importance. Traditional attempts to provide pretransplantation therapy for this group of patients have centered on the use of conventional induction chemotherapy, a process which may not be tolerated by those of advanced age or with significant other comorbidities. The demonstration of the utility of azacitidine (AZA) and other hypomethylating (HMA) agents for the treatment of higher risk MDS in recent years [1,2] has provided an alternative approach to pretransplantation induction therapy. Potential advantages include decreased toxicity and provision of time while an appropriate HLA-matched donor is identified. The impact of pre-HSCT AZA has been assessed in a limited number of studies [3-7], but these are retrospective and most include small numbers of patients. Overall, these appear to demonstrate similar overall survival (OS), relapse-free survival (RFS), relapse, and nonrelapse mortality (NRM) in patients receiving AZA compared with those who received traditional induction chemotherapy. To contribute to the debate in this area, we conducted a large retrospective analysis of patients with advanced MDS referred to the European Society for Blood and Marrow Transplant Research (EBMT) registry between 2004 and 2011.

METHODS

The EBMT data set was retrospectively analyzed to assess the outcomes of patients receiving HMA compared with those treated with conventional chemotherapy (CC) before HSCT. HMA was approved in early 2000; consequently, we selected MDS patients who received their first allogeneic stem cell transplantation between 2004 and 2011 reported to the EBMT. To include a homogeneous group of patients with blasts at time of diagnosis, we included only patients classified as having either refractory anemia with excess blasts or refractory anemia with excess blasts in transformation at time of diagnosis, with sufficient data on anthracycline-containing chemotherapy (n = 132) or HMA (n = 77). As the aim was to compare conventional induction chemotherapy with HMA, patients receiving only cytarabine (ara-C) were excluded from the analysis.

Variables analyzed included remission status at time of HSCT, donor type (HLA-identical sibling versus unrelated donor), conditioning type (myeloablative [MAC] versus reduced-intensity [RIC]), age, calendar period of transplantation, the presence of normal versus abnormal cytogenetics (*normal* being defined as 46 XX or XY and *abnormal* as all other karyotypic abnormalities), and international prognostic scoring system (IPSS) score [8] at diagnosis and at time of transplantation. Because of the recent introduction of the Revised International Prognostic Scoring System (IPSS-R) [9], patients were additionally classified according to this model and results analyzed according to IPSS-R category.

Statistical Methodology

OS was defined as time between transplantation and death or last follow-up for patients alive (censored). *RFS* was defined as time between transplantation and first relapse or death without relapse, or last follow-up for patients alive relapse-free (censored). OS and RFS probabilities were estimated by the Kaplan-Meier estimator and compared in univariate analysis by the log-rank test. Relapse and nonrelapse death were analyzed as competing risks, the cumulative incidence rates were estimated applying the proper nonparametric estimator, and the univariate comparisons were done using the Gray test. All variables considered in univariate analysis were candidates to enter the multivariate model as adjustment factors, together with the treatment group. The latter was retained even if not significant, and for the others, only the significant variables were included in the final model. All endpoints were analyzed in multivariable analysis applying Cox regression. The difference of characteristics between groups were assessed by the Fisher exact test or the chi-squared test (categorical variables) or by the Mann-Whitney or Kruskal-Wallis test (continuous variables).

RESULTS

Patients

Patient characteristics for the 2 groups are presented in Table 1. The median follow-up of the cohort was 22.1 months (95% confidence interval [CI], 16.8 to 31.3) and the median age of the population was 57.6 years (range, 20.0 to 69.6). The majority of patients were male (n = 120, 57.4%) and 37% of the population was older than 60 years. Seventy-seven patients (37%) received HMA and 132 (63%) received CC. Donors were HLA identical in 92 (44%) and matched unrelated in 117 (56%). One hundred twenty-four (59%) patients received a RIC HSCT. At the time of HSCT, 55% of patients were in complete remission (CR), with 32% not in morphological CR and 13% of patients with primary refractory disease. Of note, there were more patients in the CC group in CR at the time of HSCT (68% in CC group versus 32% in HMA group, $P < .001$). When comparing the median age between the 2 groups, although the difference in medians is small (56.8 versus 58.8), the CC group had significantly more younger patients ($P = .024$) than the HMA group. There were no significant differences between the 2 groups with regard to gender, type of donor (sibling versus HLA-matched unrelated donor), type of transplantation conditioning (MAC versus RIC),

Table 1
Patient Characteristics

Characteristic	HMA	CC	*P* Value
Patients, n	77 (37)	132 (63)	
Age, median (range), yr	58.8 (24.9-69.6)	56.8 (20.0-69.2)	.024
Gender			.773
Male	43 (56)	77 (58)	
Female	34 (44)	55 (42)	
Stage at HSCT			.001
CR	25 (32)	90 (68)	
No CR	37 (48)	29 (22)	
Primary refractory	15 (20)	13 (10)	
Donor			.204
HLA sibling	29 (38)	63 (48)	
MUD	48 (62)	69 (52)	
Conditioning			.090
MAC	25 (32)	60 (45)	
RIC	52 (68)	72 (55)	
Cytogenetics			.509
Normal	32 (43)	60 (49)	
Abnormal	42 (57)	62 (51)	
IPSS at diagnosis			.444
Low/int-1	16 (25)	16 (17)	
Int-2	27 (42)	43 (45)	
High	21 (33)	36 (38)	
IPSS at HSCT			.005
Low/int-1	13 (34)	41 (65)	
Int-2	13 (33)	8 (13)	
High	13 (33)	14 (22)	
IPSS-R			
Good	32 (46)	72 (62)	.009
Intermediate	18 (26)	21 (18)	.267 (monotonic)
Poor	15 (22)	9 (8)	
Very poor	4 (6)	14 (12)	
Treatment period			<.001
2004-2007	3 (4)	29 (22)	
2007-2009	29 (38)	52 (39)	
2009-2011	45 (58)	51 (39)	

MUD indicates matched unrelated donor; int, intermediate.
Data presented are n (%), unless otherwise indicated.

percentage of patients with normal cytogenetics, or IPSS score at diagnosis. In contrast, for the IPSS score at HSCT, the CC group had fewer patients with high or intermediate-2 IPSS and more patients with low IPSS compared with the HMA group ($P = .005$). Analysis of treatment calendar period divided into those treated before 2007 and those treated after 2007 indicated that a greater proportion of patients treated with HMA (96% of HMA patients versus 78% of CC patients) were treated after 2007 ($P < .001$).

Survival, Relapse, and NRM

OS and RFS did not differ between the 2 groups (Figure 1), with an estimated 3-year OS and RFS of 41% (95% CI, 31% to 51%) and 36% (95% CI, 27% to 46%) for the CC group and 42% (95% CI, 26% to 57%) and 29% (95% CI, 16% to 42%) for the HMA group, respectively. The cumulative incidence of relapse (CIR) was 38% at 3 years for the CC group and 45% for the HMA group ($P = .633$, Gray test) (Figure 1). Similarly, there was no significant difference in NRM between the 2 groups, with NRM at 3 years being 26% in the HMA group (95% CI, 14% to 38%) and 26% in the CC group (95% CI, 18% to 35%). On univariate analysis, when compared with patients in CR, those with primary refractory disease had worse outcome in terms of OS and RFS (hazard ratio [HR], 2.42; 95% CI, 1.41 to 4.13; $P = .00$ for OS and HR, 2.27; 95% CI, 1.37 to 3.76; $P = .001$ for RFS) (Figure 2). In terms of overall relapse risk, there was no significant difference for those with primary refractory disease when compared to those in CR ($P = .30$), though in terms of instantaneous risk, there is a significant difference (Cox model: HR, 2.09; 95% CI, 1.05 to 4.16; $P = .035$). This difference is explained by the significantly higher risk of NRM in those with primary refractory disease (HR, 2.49; 95% CI, 1.18 to 5.26; $P = .016$). Patients not in CR but without primary refractory disease had similar outcomes compared with those in CR. Donor type, conditioning regimen (MAC versus RIC), presence of normal versus abnormal cytogenetics, and IPSS at diagnosis or at HSCT did not affect OS, RFS, CIR, or NRM. Additionally, no statistically significant effect on outcomes was noted in regard to age (analyzed as a continuous variable) or calendar period of HSCT.

Effect of IPSS-R Cytogenetic Grouping

Adequate data were available in 185 of the 209 patients to be able to classify patients according to IPSS-R cytogenetic grouping (Table 1). Using this classification, no differences in HMA and CC groups in regard to IPSS-R cytogenetic risk group were identified; however, numbers in the poor (n = 24) and very-poor (n = 18) categories were small. In view of this, these categories were combined for further analysis, revealing a greater proportion of patients with worse IPSS-R in the HMA group than in the CC group ($P = .06$). Although not monotonic when considering the good and intermediate groups, significant differences were apparent with regard to the use of cytogenetic risk groups with poorer outcomes demonstrated in the poor/very poor categories. The 3-year OS and RFS in the very poor/poor group were 28% (95% CI, 11% to 45%) and 12% (95% CI, 0 to 25%), respectively, compared with 55% (95% CI, 37% to 74%) and 50% (95% CI, 33% to 68%) in the intermediate group, and 43% (95% CI, 31% to 56%) and 35% (95% CI, 23% to 46%) in the good-risk group. Reasons for better outcomes in the intermediate than in the good-risk group are attributable to worse NRM in the good-risk group. NRM at 3 years in the good-risk group was 32% (95% CI, 21% to 42%) compared with 14% (95% CI, 3% to 26%) in the intermediate-risk group. For relapse, outcomes worsened with increasing cytogenetic risk category: 3-year relapse rates were 34% (95% CI, 23% to 45%), 36% (95% CI, 19% to 52%), and 61% (95% CI, 44% to 78%) for good, intermediate, and poor/very poor categories, respectively.

Multivariate Analysis

In multivariate analysis (Table 2), the effect of primary refractory disease on outcomes when compared with patients in CR was retained as described in the univariate analysis: HR for OS, 2.93 (95% CI, 1.63 to 5.27; $P < .001$), HR for RFS, 2.56 (95% CI, 1.48 to 4.45; $P = .001$), HR for relapse, 2.32 (95% CI, 1.10 to 4.88; $P = .027$), and HR for NRM, 2.9 (95% CI, 1.28 to 6.58; $P = .011$). Inclusion of the IPSS-R (Table 2) in the model (when compared to good) influenced RFS and relapse but not other outcomes: HR for RFS, 1.61 (95% CI, 1.03 to 2.52; $P = .038$) and HR for relapse, 2.33 (95% CI, 1.31 to 4.14; $P = .004$). It is to be noted that the role of refractory disease becomes insignificant in the multivariate model for relapse when IPSS-R cytogenetic risk groups are included.

DISCUSSION

Herein, we present the results of a large retrospective analysis by the Chronic Malignancies Working Party of the EBMT demonstrating equivalent outcomes for either

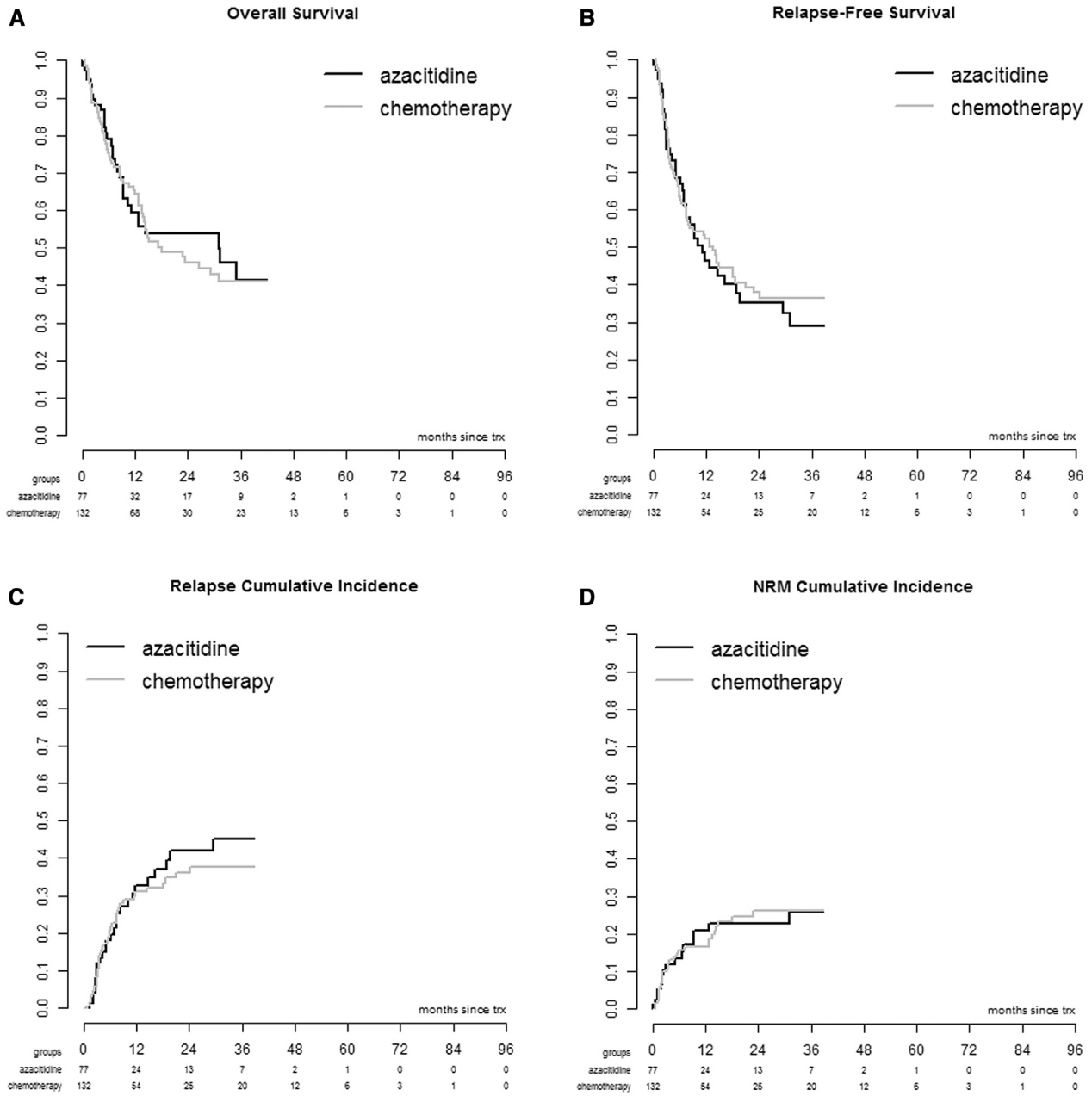

Figure 1. Outcomes for hypomethylating agents compared with chemotherapy. (A) Shows overall survival, (B) relapse-free survival, (C) cumulative incidence of relapse, and (D) nonrelapse mortality.

pretransplantation HMA or CC. This is particularly notable, given the low number of patients in the HMA group who achieved CR and the younger age of those in the CC group. In addition, there was a slight increase in the proportion of those with worse cytogenetics per the IPSS-R classification in the HMA group. Previous studies have also demonstrated similar equivalence of these 2 modalities of pretransplantation induction therapy, although only 1 directly looking at this issue is of a similar size [4]. In that study, the reported 3-year OS and RFS rates for HMA and CC (58% versus 51% for OS and 52% versus 45% for RFS) were higher than those reported here (42% versus 41% for OS, and 29% versus 36% for RFS). The reasons for this difference are unclear; however, they are likely to reflect differences between the 2 patient populations. For example, in the Damaj study, 74% of patients were reported to have $< 5\%$ blasts before HSCT compared with only 55% of patients in our study considered to be in CR. Overall outcomes are similar to that reported by other groups of outcomes after HSCT for advanced MDS [7,10,11].

The recent publication of the cytogenetic scoring system used in IPSS-R [12] provided an improved method of predicting outcomes for patients with MDS in both general and transplantation settings [13,14]. None of the other analyses of pretransplantation HMA have included this scoring system; hence, we attempted to review its utility in our patient cohort. Although small numbers meant the poor and very poor groups had to be combined for analysis, we

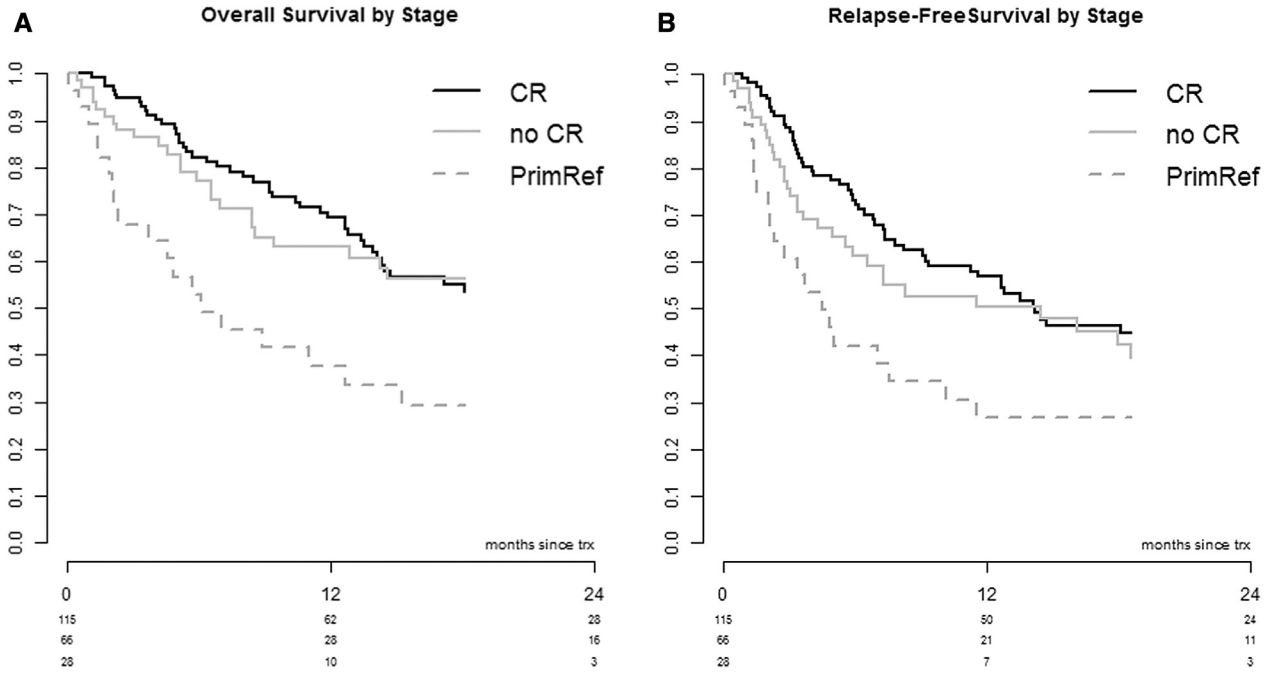

Figure 2. Outcomes according to disease status before HSCT. (A) Shows overall survival and (B) shows relapse-free survival.

demonstrate a significant adverse effect of adverse cytogenetics on relapse and RFS, underlying the importance of considering the pretransplantation karyotype on prognosis. The relapse incidence of 61% at 3 years in these patients, along with currently reported poor outcomes in those who relapse after transplantation [15,16], indicates the urgent need for strategies directed at prevention of post-HSCT relapse.

The influence of CR status is interesting. A minimal pretransplantation disease burden is considered important for post-transplantation outcomes [17,18], and the presence of more than 5% blasts at time of HSCT is reported to contribute to poor results [19]. Whether this reflects the pretransplantation therapy or an inherent biological sensitivity that is more likely to result in favorable outcomes after HSCT remains uncertain. In our analysis, 48% of the HMA group and 22% of the CC group were not in CR at the time of HSCT. Unlike for patients with primary refractory disease, on univariate analysis, the outcomes of patients not in CR could not be demonstrated to be significantly worse than those in CR before HSCT. This potentially explains the equivalent outcomes in the HMA and CC groups despite the higher proportion of patients not in CR in the HMA group at the time of HSCT. A recent publication by a French group demonstrated no difference in post-HSCT outcomes when AZA was compared with the best supportive care before HSCT [20]. Furthermore, given evidence that a number of patients potentially suitable for transplantation submitted to preinduction therapy do not reach transplantation [21], it may be that an upfront HCST approach is preferable for selected patients. This further complicates an area where, for many groups, some form of pretransplantation induction therapy is now considered standard. Although beyond the scope of our study, prospective delineation of factors that identify the most appropriate type of pretransplantation therapy are required. In the absence of these, a recently published algorithm contributes further to this debate [22].

On multivariate analysis, the major factor affecting outcomes was the presence of primary refractory disease, although worsening IPSS-R cytogenetics could be demonstrated to have an effect of RFS and CIR. The adverse effect of primary refractory disease is in line with that reported in other studies. Notably, these patients had an increased NRM and it is possible that there is no advantage for ongoing attempts at induction therapy for this subgroup of patients if the only result is increased toxicity. Novel transplantation approaches and/or the use of directed therapy, such as post-HSCT donor lymphocyte infusion, are required to improve outcomes in these patients. The adverse effect of worsening IPSS-R cytogenetics in our analysis was limited by small numbers; however, a recently published large EBMT analysis confirms the impact of IPSS-R cytogenetics on OS and CIR and additionally on OS [14]. That study also reported a significant effect of monosomal karyotype within the poor risk category, a factor that could not be analyzed in this study.

Although this study includes a large number of patients, it is limited by the retrospective nature of the analysis and some missing data points. Because we only have information on those patients who underwent transplantation, we do not attempt to draw conclusions on all patients treated and, therefore, are unable to provide information on outcomes of patients who received either HMA or CC but failed to proceed to transplantation. Furthermore, it is not known why centers decided for CC or HMA and detailed information on comorbidities influencing the choice of pre-HSCT therapy was not available.

In conclusion, despite the above limitations, this large study provides further weight with regard to the accumulating evidence that pre-HSCT HMA or CC results in equivalent post-transplantation outcomes. Furthermore, we suggest that other prognostic factors such as adverse cytogenetics or primary refractory disease are far more relevant to outcome than type of prior transplantation therapy. Prospective trials with accompanying translational studies are

Table 2
Results of Multivariate Analysis

Outcome	HR	*P* Value	95% CI
Overall survival			
Treatment			
HMA	1.00	—	—
CC	1.33	.274	.80-2.22
Stage			
CR	1.00	—	—
No CR	1.42	.184	.85-2.39
Primary refractory	2.71	.002	1.43-5.16
IPSS-R			
Good	1.00	—	—
Int	.67	.192	.37-1.22
Poor/very poor	1.45	.145	.88-2.39
RFS			
Treatment			
HMA	1.00	—	—
CC	1.12	.638	.70-1.78
Stage			
CR	1.00	—	—
No CR	1.43	.131	.90-2.29
Primary refractory	2.22	.010	1.21-4.06
IPSS-R			
Good	1.00	—	—
Intermediate	.65	.126	.37-1.13
Poor/very poor	1.61	.038	1.03-2.52
NRM			
Treatment			
HMA	1.00	—	—
CC	1.31	.474	.63-2.71
Stage			
CR	1.00	—	—
No CR	1.36	.432	.63-2.92
Primary refractory	3.07	.012	1.29-7.35
IPSS-R			
Good	1.00	—	—
Intermediate	.40	.062	.15-1.05
Poor/very poor	.95	.888	.44-2.02
Relapse			
Treatment			
HMA	1.00	—	—
CC	.98	.945	.54-1.78
Stage			
CR	1.00	—	—
No CR	1.46	.206	.81-2.65
Primary refractory	1.63	.259	.70-3.80
IPSS-R			
Good	1.00	—	—
Intermediate	.89	.733	.44-1.77
Poor/very poor	2.33	.004	1.31-4.14

required to confirm these results and provide further information with regard to individual factors that may direct the most appropriate choice of pretransplantation therapy.

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