Biol Blood Marrow Transplant 25 (2019) 1550–1559

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Comparison between Upfront Transplantation and different Pretransplant Cytoreductive Treatment Approaches in Patients with High-Risk Myelodysplastic Syndrome and Secondary Acute Myelogenous Leukemia

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Article history:
Received 28 January 2019
Accepted 11 March 2019

Key Words:
Myelodysplastic syndromes
Secondary AML
Transplantation
Upfront
Cytoreduction
Chemotherapy
Hypomethylating agents

A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for patients with advanced myelodysplastic syndrome (MDS) and secondary acute myelogenous leukemia (sAML), but in the absence of prospective trials the impact of pretransplant cytoreduction is controversially discussed. We retrospectively analyzed the outcome of 165 patients with MDS and excess blasts (n = 126, 76%) and sAML (n = 39, 24%) according to a pretransplant strategy. Sixty-seven patients (41%) were directly transplanted (upfront group), whereas 98 patients (59%) had received pretransplant cytoreductive treatment (induction chemotherapy [CTX], n = 64; hypomethylating agents [HMAs], n = 34) resulting in a significantly higher complete remission rate in the CTX group (59% versus HMA 18%, $P < .0001$). Estimated rates of 5-year overall survival (OS) and relapse-free survival (RFS) for the entire group were 54% and 39%, respectively. The 5-year OS rates of the upfront, CTX, and HMA groups were 61%, 50%, and 45%, respectively ($P = .116$), whereas RFS rates were 38%, 41%, and 38% ($P = .926$). Cumulative incidence of relapse (CIR) and nonrelapse mortality (NRM) did not differ between treatment groups. In the upfront group no difference regarding OS and RFS was seen with respect to pretransplant blast count (>10% versus <10%). In multivariate analyses type of pretransplant strategy did not have an effect on OS, RFS, CIR, and NRM, whereas cytogenetics (OS, RFS, CIR), reduced-intensity conditioning (OS, RFS, CIR), and an unrelated donor (RFS, CIR) were identified as negative predictors. When compared with the upfront group, 5-year OS was significantly lower in patients with CTX-refractory disease (34% versus 64%, $P = .0346$) and by clear trend in HMA nonresponders (42% versus 61%, $P = .073$), whereas RFS did not differ significantly. In further support of the concept, that pretransplant therapy may favor the selection of resistant clones, patients in the upfront group had a higher likelihood to respond to HMAs as salvage therapy for relapse in comparison with pretreated patients (complete remission, 58% versus 10%; $P = .0005$) and a higher 2-year OS rate after relapse (59% versus 19%, $P = .0001$). These data suggest that an upfront transplant strategy is at least not inferior to pretransplant cytoreduction and may be augmented by HMAs + donor lymphocyte infusion salvage therapy in case of relapse after allo-HSCT.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment option for patients with myelodysplastic syndromes (MDS) and acute myelogenous leukemia derived from MDS (sAML) [1,2]. However, there is controversy among experts if and how patients with MDS should receive cytoreductive "debulking" chemotherapy (CTX) before transplant. MDS patients without elevated bone marrow (BM) blast counts usually proceed to transplant without cytoreduction, whereas patients with MDS and excess blasts and those with sAML often receive cytoreductive treatment to achieve remission before transplant [1,3]. Cytoreduction before allo-HSCT may be achieved either by traditional AML-like induction CTX or, in the last decade, also by treatment with the

Financial disclosure: See Acknowledgments on page 1558.
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https://doi.org/10.1016/j.bbmt.2019.03.011
1083-8791/

hypomethylating agents (HMAs) azacitidine (Aza) or decitabine (DAC) [4-8]. The common goals of these cytoreductive strategies are to bridge the time to transplantation and to reduce disease burden to prevent relapse after transplant [1-3]. Nevertheless, pretransplant cytoreduction is associated with several drawbacks, because it is associated with a considerable risk for early mortality and potentially severe toxicity, preventing patients to proceed to transplant. Furthermore, remission rates after induction CTX and, in particular, HMAs are limited [4-10].

Indeed, the question is whether one needs to apply cytoreductive therapies before transplant at all or may circumvent some of the associated risks by proceeding directly to transplantation. Sequential conditioning strategies such as fludarabine, amsacrine, and cytarabine (FLAMSA)-based reduced-intensity conditioning (RIC) and even myeloablative conditioning (MAC) regimens combine intensive AML-like induction CTX and conditioning early during the course of disease [11-13]. So far this issue has not been tested in prospective randomized trials, and retrospective reports have not shown a clear advantage of any of these 3 approaches. Furthermore, most published retrospective analyses compared only 2 modalities with each other [14-21]. To contribute to this debate, we retrospectively analyzed the outcome of patients with MDS and sAML transplanted at our center according to the pretransplant strategy.

METHODS

Patients

Between 1999 and 2016 a total of 213 consecutive patients with MDS or sAML received an allo-HSCT at our institution. To compare pretransplant cytoreductive strategies (either induction CTX or HMAs) with the concept of upfront transplantation in a homogeneous group of patients, we included only those 165 patients with a BM blast count of ≥5% at diagnosis, because this threshold represents a potential indication for cytoreductive therapy (Supplementary Figure S1). The decision of whether cytoreductive therapy prior transplant or direct transplantation was performed was made individually for every patient. The major discriminator between upfront transplant and cytoreduction was the fast availability of a suitable stem cell donor at the time of referral to our center. In those patients who were referred to us directly at diagnosis, the primary intention was to perform an upfront transplant when prompt donor availability was given. In patients referred by other physicians during the course of the disease, the decision regarding pretransplant therapy was primarily made by the referring physician. Parameters regarding demographics, pretransplant treatment, transplant procedures, and outcome data were retrospectively analyzed with a data lock in August 2017.

Definitions

Diagnoses of patients were categorized according to the 2008 World Health Organization classification and risk classification according to the International Prognostic Scoring System [22] by disease characteristics at diagnosis. Induction CTX consisted at least of a combination of an anthracycline and cytarabine, whereas patients in the HMA group had received at least 1 cycle of Aza or DAC. Patients in the upfront group had not received any therapy for MDS and sAML with the exception of transfusions, growth factors, or a short course of hydroxyurea in individual patients. Complete remission (CR) after induction CTX or HMAs was defined as previously described [23], as was the classification of conditioning intensity [24].

Statistical Analysis

Patient characteristics as continuous variables were summarized using median (range), whereas for categorical variables frequency tables were used. For univariate comparison of potential differences, cross-tabulation, Fisher's exact test, and Mann-Whitney test were used. Overall survival (OS) was defined as time from transplantation until death or date of last follow-up in surviving patients. Relapse-free survival (RFS) was defined as time between transplantation and relapse or death without relapse. Patients who were alive and had not relapsed until last follow-up were censored at this date. Time-to-event curves for OS and RFS were calculated using the Kaplan-Meier method, and log-rank test was used for univariate comparisons. Relapse incidence and nonrelapse mortality (NRM) were considered as competing risks and were calculated using cumulative incidence estimates using the Gray test for univariate comparisons. Factors influencing OS and RFS or response in univariate analysis with $P < .10$ were included into multivariate analysis. For OS and RFS, a Cox regression model was used with a stepwise backward procedure deleting factors in the final model above the cut-off significance level of .05. For relapse incidence and NRM variables the multivariate models were interpreted as a cause-specific hazards model. Backward selection using the Akaikes information criterion was applied. The type of pretransplant strategy (upfront transplantation, CTX, or HMAs) was included in all multivariate analyses even if not significant in univariate analyses. Statistical analyses were performed using Prism 5.01 (GraphPad Software Inc, La Jolla, CA), SPSS for Windows (SPSS Inc, Chicago, IL), and R 3.4.4 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and Treatment

According to their pretransplant strategy we analyzed data of 165 consecutive patients (median age, 55 years; range, 21 to 72) with MDS and MDS/myeloproliferative neoplasm overlap syndrome (n = 126, 76%) with a BM blast count of ≥5% at diagnosis or sAML (n = 39, 24%) who had received an allo-HSCT at our institution between 1999 and 2016. Of these, 67 patients (41%) directly proceeded to allo-HSCT without pretreatment (upfront group). Sixty-four patients (39%) received 1 or 2 cycles of an anthracycline-containing induction CTX (CTX group) before transplantation, which resulted in CR in 59% (n = 38), whereas 26 patients were primary refractory (41%). The remaining 34 patients (20%) received a median of 4 cycles (range, 1 to 8) of HMA (Aza, n = 32; DAC, n = 1; Aza followed by DAC, n = 1) before allo-HSCT (HMA group), which induced CR in 6 patients (18%). The CR rate was significantly higher in patients receiving induction CTX compared with those treated with HMAs (59% versus 18%, $P < .0001$) (Supplementary Figure S1, Table 1).

Details on patient characteristics and transplantation are given for all patients and separately for the 3 treatment groups in Table 1. Patients in the upfront group were significantly younger and suffered more frequently from chronic myelomonocytic leukemia than those in the CTX and HMA groups. Furthermore, there were significantly more patients in the upfront group suffering from a therapy-related myeloid neoplasm in comparison with those patients who had received induction CTX. During the interval from diagnosis to transplant, 26 patients (39%) in the upfront group progressed to an advanced disease stage, including 7 patients (10%) with transformation to AML. Patients in the CTX group were significantly younger than those treated with HMAs and more often suffered from sAML compared with the 2 other treatment groups. No differences were found between the 3 treatment groups with regard to gender, karyotype abnormalities, and International Prognostic Scoring System stage (Table 1).

Allo-HSCT was performed at a median of 5.7 months (range, 1 to 177) after diagnosis. Time from diagnosis to transplant did not differ significantly between the 3 treatment groups (upfront group median 4.9 months versus CTX group 6.4 months versus HMA group 6.3 months). Most patients (72%) received grafts from unrelated donors, and RIC was applied before stem cell infusion in 68% of patients. Probably as a consequence of the age differences, a higher proportion of patients in the HMA group (85%) received a RIC regimen compared with the other groups. A sequential conditioning approach incorporating FLAMSA-based CTX was used in 62% of patients. Significantly more patients in the upfront (73%) and HMA (68%) groups received FLAMSA-based conditioning, because in these 2 treatment groups significantly more patients were not in remission at the time of transplant. Detailed information regarding the conditioning regimens are given for all patients and separately for the 3 treatment groups in Supplementary Table S1.

Table 1
Patient Demographics and Disease and Transplant Characteristics

	all patients	upfront	CTX	HMA	p value
No.	165	67	64	34	
Age (years), median (min, max)	55 (21-72)	52 (21-68)	57 (26-72)	62 (42-72)	*0.0451 **<0.0001 ***0.0073
Sex, n (%)					
Male	111 (67%)	42 (63%)	46 (72%)	23 (68%)	
Female	54 (33%)	25 (37%)	18 (28%)	11 (32%)	
WHO 2008 category at diagnosis, n (%)					
RAEB I	43 (26%)	28 (42%)	8 (12%)	7 (21%)	
RAEB II	60 (36%)	19 (28%)	20 (31%)	21 (61%)	#0.07
CMML I+II	19 (12%)	13 (19%)	5 (8%)	1 (3%)	##0.0309
MDS/MPN unclassifiable	4 (2%)	2 (3%)	1 (2%)	1 (3%)	###<0.0001
AML with MDS-related changes	39 (24%)	5 (8%)	30 (47%)	4 (12%)	####0.0007
Therapy-related, n (%)					
yes	35 (21%)	22 (33%)	6 (9%)	7 (21%)	§0.0012
no	130 (79%)	45 (67%)	58 (91%)	27 (79%)	
IPSS at diagnosis, n (%)					
low/int-1	23 (20%)	13 (26%)	7 (19%)	3 (11%)	
int-2	51 (45%)	27 (54%)	12 (33%)	12 (43%)	
high	40 (35%)	10 (20%)	17 (48%)	13 (46%)	
Karyotype, n (%)					
normal	56 (37%)	22 (36%)	26 (44%)	8 (25%)	
abnormal	97 (63%)	39 (64%)	34 (56%)	24% (75%)	
Poor-risk cytogenetics, n (%)					
yes	59 (39%)	25 (41%)	21 (35%)	13 (41%)	
no	94 (61%)	36 (59%)	39 (65%)	19 (59%)	
Remission state at transplant, n (%)					
CR	34 (21%)	0	38 (59%)	6 (18%)	&<0.0001
no CR	131 (79%)	67 (100%)	26 (41%)	28 (82%)	
Median Time from diagnosis to transplant, months	5.7	4.9	6.4	6.3	
min, max	1.0-177.2	1.02-67.9	1.6-177.2	3.0-50.3	
Conditioning, n (%)					$0.0013
reduced-intensity	113 (68%)	41 (61%)	43 (67%)	29 (85%)	$$0.06
standard-dose	52 (32%)	26 (39%)	21 (33%)	5 (15%)	$$$0.0025
FLAMSA-based	102 (62%)	49 (73%)	30 (47%)	23 (68%)	$$$$0.06
Donor, n (%)					
related	47 (28%)	19 (28%)	22 (34%)	6 (18%)	
unrelated	118 (72%)	48 (72%)	42 (66%)	28 (82%)	

CMML indicates chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System; MPN, myeloproliferative neoplasm; RAEB, refractory anemia with excess blasts; WHO, World Health Organization.
*Significant differences between the untreated and CTX groups.
**Significant differences between the untreated and HMA groups.
***Significant differences between the HMA and CTX groups.
#Differences regarding the frequency of CMML between the untreated and CTX groups.
##Significant differences regarding the frequency of CMML between the untreated and HMA groups.
###Significant differences regarding the frequency of sAML between the untreated and CTX groups.
####Significant differences regarding the frequency of sAML between the HMA and CTX groups.
§Significant differences regarding the frequency of therapy-related MDS between the untreated and CTX.
&Significant differences regarding the CR rate between the HMA and CTX groups.
$Significant differences regarding the use of RIC between the untreated and HMA groups.
$$Differences regarding the use of RIC between the CTX and HMA groups.
$$$Significant differences regarding the use of FLAMSA-based conditioning between the untreated and CTX groups.
$$$$Differences regarding the use of FLAMSA-based conditioning between the HMA and CTX groups.

Outcome after Allo-HSCT According to Pretransplant Treatment

After a median follow-up of 23 months (range, 1 to 202), the estimated 5-year OS, RFS, CIR, and NRM probabilities of the entire cohort were 54% (95% confidence interval [CI], 46% to 63%), 39% (95% CI, 31% to 46%), 44% (95% CI, 37% to 53%), and 16% (95% CI, 11% to 23%), respectively (Figure 1A-C). Comparing the outcome after transplant according to the pretransplant strategy, we did not observe a significant difference regarding OS (5-year OS: upfront 61% [95% CI, 50% to 75%], CTX 50% [95% CI, 38% to 63%], and HMA 45% [95% CI, 27% to 64%]; $P = .116$), RFS (5-year RFS: upfront 38% [95% CI, 26% to 49%], CTX 41% [95% CI, 28% to 53%], and HMA 38% [95% CI, 20% to 56%]; $P = .926$), CIR (5-year CIR: upfront 46% [95% CI, 30% to 66%], CTX 42% [95% CI, 31% to 56%], and HMA 47% [95% CI, 35% to 60%]; $P = .89$), and NRM (5-year NRM: upfront 16% [95% CI, 9% to 26%], CTX 18%

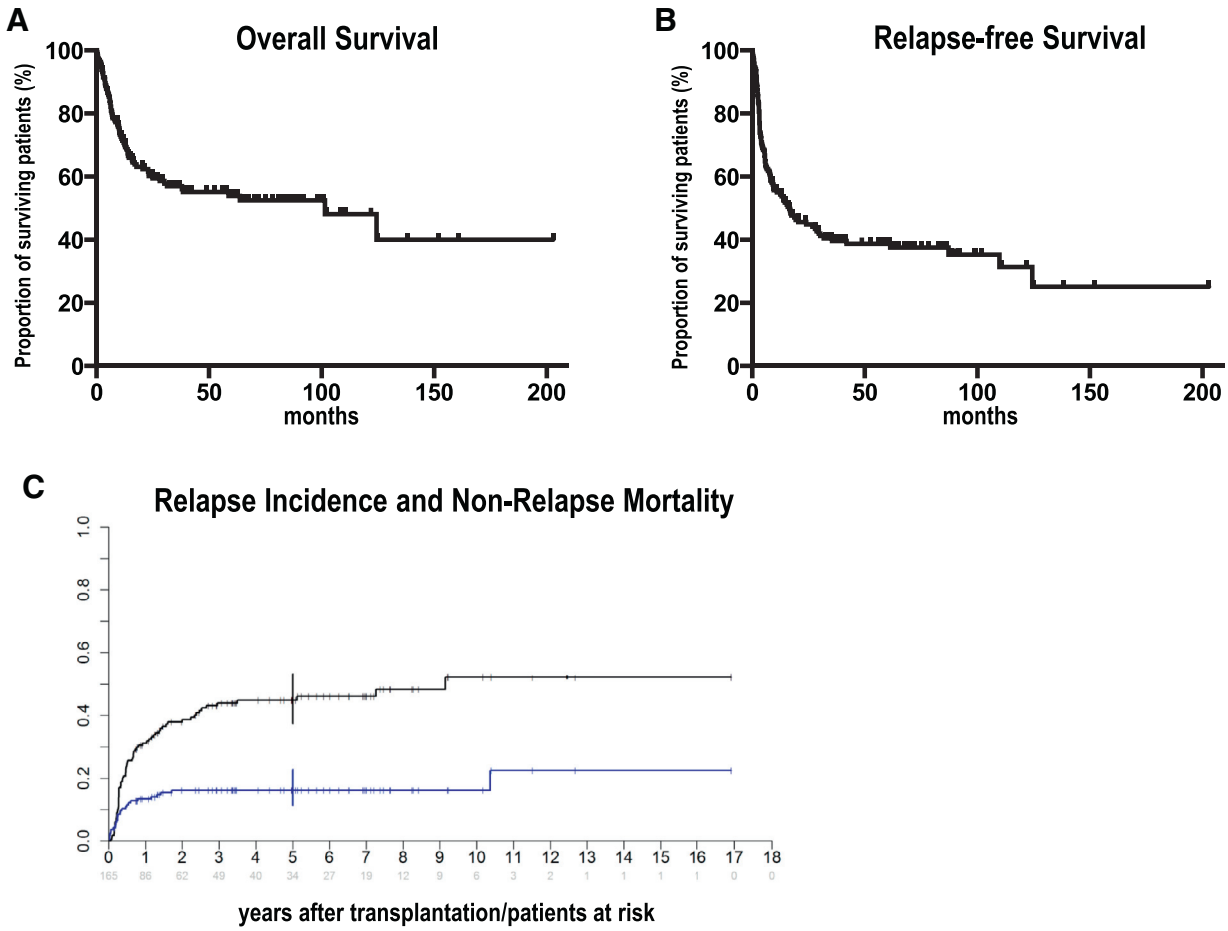

Figure 1. Outcome after allo-HSCT of the entire cohort (N = 165). (A and B) OS and RFS. (C) CIR (black curve) and NRM (blue curve).

[95% CI, 10% to 29%], and HMA 15% [95% CI, 9% to 26%]; $P = .90$) between the 3 treatment groups (Figure 2A-D, Table 2). This also applied when focusing only on those patients with ≥10% marrow blasts (Supplementary Figure S2).

The 5-year OS was significantly lower in patients refractory after CTX (34% versus 61%, $P = .0346$) and by clear trend in patients not responding to HMAs (42% versus 61%, $P = .073$) compared with the upfront group, whereas we were not able to find significant differences regarding 5-year RFS between patients refractory after CTX (22% versus 38%, $P = .189$) and respectively those not responding to HMAs (34% versus 38%, $P = .572$) compared with the upfront group (Figure 3A-D). In line with this finding, when considering patients with ≥5% BM blasts at the time of transplant, 5-year OS was significantly higher (61% versus 41%, $P = .0311$) in previously untreated patients (median BM blast count, 15%; range, 5% to 70%) than in pretreated patients (median BM blast count, 15%; range, 5% to 80%; $P = .2604$), whereas 5-year RFS did not differ (36% versus 30%, $P = .223$) (Figure 4A,B).

Because a panel of international experts recently recommended performing pretransplant cytoreduction at least in those MDS patients with a BM blast count of ≥10% [1], we analyzed the outcome of patients in the upfront group according to their BM blast count. By dichotomizing the patients in the upfront group according to this arbitrary cut-off of 10% blasts, we did not find any difference in terms of OS and RFS (Figure 4C,D).

Predictors for Outcome

Besides the type of pretransplant therapy, we also tested multiple patient and disease characteristics as well as transplant-related factors with regard to their impact on post-transplant outcome (Table 2). In univariate analysis we identified the presence of an abnormal karyotype, poor-risk cytogenetics [22], and age (defined as above the median of 55 years) as factors that adversely influenced OS, whereas the use of a MAC regimen was associated with a better OS. The same patient- and disease-related factors (abnormal karyotype, poor-risk cytogenetics, and age) and the use of an unrelated donor negatively affected RFS, whereas the choice of a MAC regimen had a positive impact on RFS. Both transplant-related factors (the use of MAC and an unrelated donor) as well as patient age and poor-risk cytogenetics significantly impacted relapse incidence in the same direction as observed with regard to RFS. No patient-, disease-, or transplant-related variables influencing NRM could be identified in the univariate analysis (Table 3).

Multivariate Analysis

In the multivariate analysis (Table 4) poor-risk cytogenetics (hazard ratio [HR], 2.63; 95% CI, 1.45 to 3.85; $P = .001$) and the use of MAC regimen (HR, .42; 95% CI, .23 to .75; $P = .002$) retained their prognostic impact on OS. Regarding RFS, poor-risk cytogenetics (HR, 2.18; 95% CI, 1.43 to 3.30; $P < .001$) and the application of a MAC regimen (HR, .502; 95% CI, .32 to .80; $P = .004$) were confirmed as determining factors as well as the

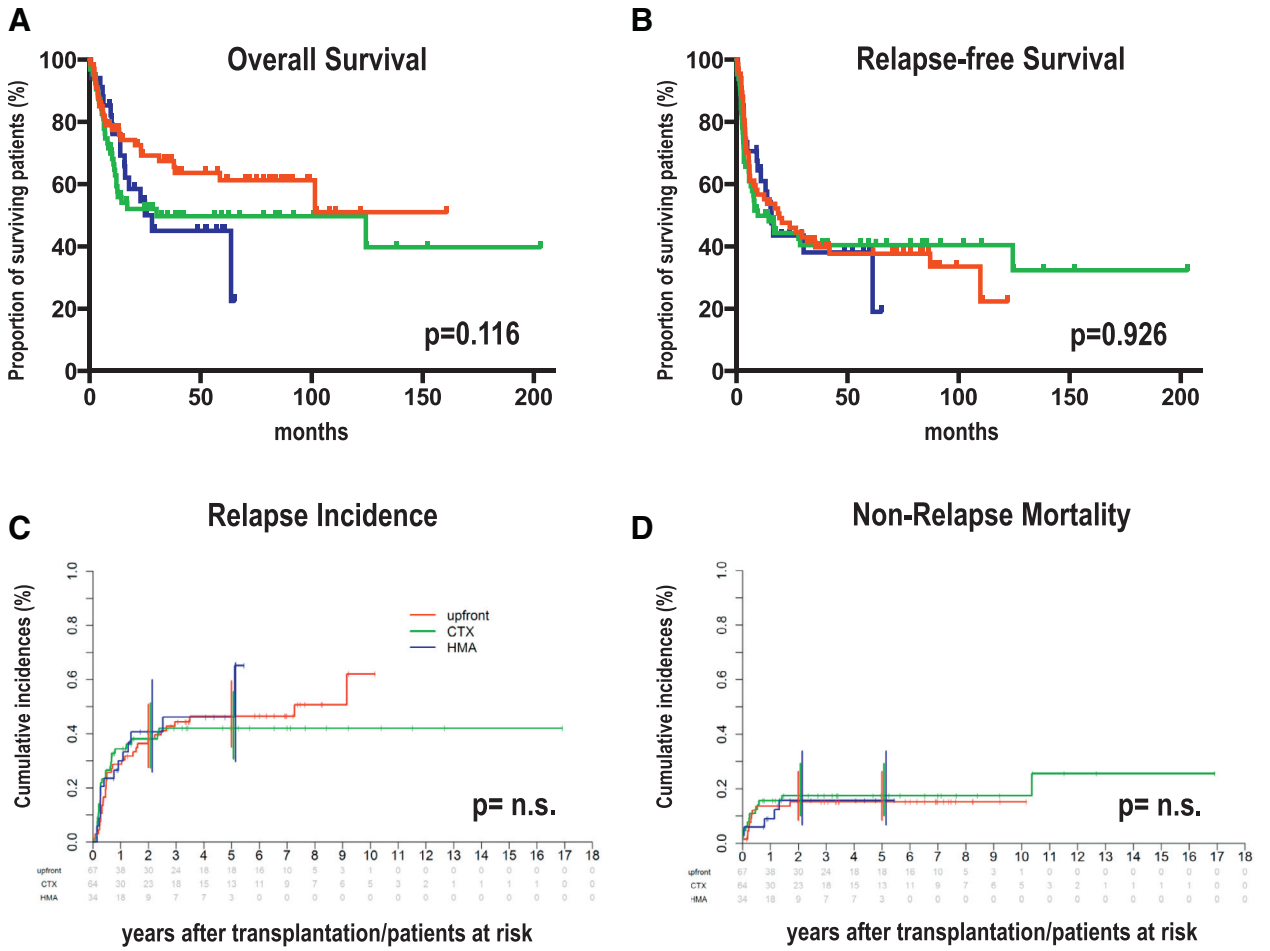

Figure 2. Outcome after allo-HSCT according to the pretransplant treatment strategy. OS and RFS (A and B), CIR (C), and NRM (D) are shown separately for patients in the upfront group (red curves) and those treated either with CTX (green curves) or HMAs (blue curves).

use of a matched related donor (HR, .49; 95% CI, .29 to .82; $P = .006$). These 3 variables were also identified as predictive for relapse incidence, whereas no parameter was found to have prognostic impact on NRM (Table 5).

Multivariate analysis confirmed the absence of significant differences between upfront transplantation and pretransplant treatment (intensive CTX or HMAs) in terms of OS, RFS, CIR, and NRM (Tables 4 and 5). This supports the notion that upfront transplantation is at least not inferior to pretransplant cytoreductive approaches.

Outcome in Patients Relapsing after alloHSCT According to Pretransplant Treatment

RFS of patients in the upfront group did not differ significantly from those of patients who were refractory to CTX or HMAs. In contrast, OS of treatment-naïve patients was comparable with OS of pretreated patients, who were in remission at the time of transplant, but significantly higher than OS of refractory patients (Figure 3). To address the hypothesis that pretransplant therapy may influence outcome in case of relapse, we analyzed response to first salvage therapy and survival of all 73 patients who relapsed after a median of 5.6 months (range, 1 to 110) after allo-HSCT. Most patients received salvage therapy with HMAs (n = 58, 79%; Aza, n = 57; DAC, n = 1), mostly in combination with donor lymphocyte infusion, whereas the remaining received other salvage treatments (intensive CTX, n = 1; donor lymphocyte infusion alone, n = 1; second transplant, n = 3; best supportive care, n = 5; miscellaneous, n = 2; missing information, n = 3; Supplementary Figure S3).

Indeed, a significantly higher proportion of patients in the upfront group (58%) achieved CR after salvage treatment with HMAs when compared to pretreated patients (10% CR, $P < .001$; CTX group, 5% CR; HMA group, 18% CR). Accordingly, OS calculated from the time of relapse was significantly superior in patients in the upfront group than in the group of pretreated patients (2-year OS, 59% [95% CI, 42% to 80%] versus 19% [95% CI, 4% to 30%], respectively; $P = .0001$; Supplementary Figure S4).

DISCUSSION

Our retrospective analysis of 165 consecutive patients with high-risk MDS and sAML demonstrates that the outcome in terms of OS, RFS, CIR, and NRM after upfront transplantation is at least not inferior when compared with patients who had received cytoreductive therapy before transplant. Furthermore, our results suggest for the first time that pretransplant treatment may impact response and survival after salvage therapy in patients who relapse after allo-HSCT. In addition, we could confirm the well-established role of poor-risk cytogenetics as a negative prognostic factor for relapse and OS [19,25,26]. Of note, we also identified the use of RIC (OS, RFS, CIR) and an unrelated donor (RFS, CIR) as negative outcome predictors.

Table 2
Univariate Analysis for OS and RFS

Variable	5-year OS	95% CI	p value	5-year RFS	95% CI	p value
IPSS			0.156			0.479
low/int-1	62%	45-87%		39%	20-58%	
int-2/high	52%	42-63%		39%	31-47%	
Cytogenetics			0.019			0.039
normal	65%	54-70%		45%	31-59%	
abnormal	47%	37-59%		35%	25-45%	
Poor-risk cytogenetics			0.001			0.001
no	63%	54-75%		45%	35-56	
yes	38%	25-51%		19%	5-29%	
BM blasts at diagnosis			0.183			0.401
<10%	61%	49-75		41%	29-54%	
>10%	50%	40-61%		38%	28-48%	
Therapy-related			0.572			0.782
no	52%	44-62%		39%	30-47%	
yes	59%	43-79%		39%	21-58%	
Age			0.041			0.06
<Median	65%	56-77%		46%	36-57%	
>Median	40%	28-53%		31%	19-41%	
Donor			0.301			0.012
related	60%	47-76%		53%	39-69%	
unrelated	51%	41-61%		31%	24-42%	
Conditioning			0.01			0.01
reduced-intensity	46%	36-57%		33%	24-42%	
standard-dose	69%	57-85%		51%	38-67%	
Type of therapy			0.116			0.926
upfront	61%	50-75%		38%	26-49%	
chemotherapy	50%	38-63%		41%	28-53%	
HMA	45%	27-64%		38%	20-56%	

The value of "debulking" cytoreductive therapy either with CTX or HMAs in patients with high-risk MDS and sAML is still not properly defined. No prospective randomized trial on this important clinical question has been published so far, and all but 1 [19] of the retrospective studies reported compared only 2 approaches within 1 analysis [14-18,20,21]. In contrast, here we were able to analyze both approaches, classic AML-like induction CTX and treatment with HMAs, and compare them with upfront transplant with sequential conditioning, thereby covering all 3 currently established strategies within 1 analysis. We included only patients with ≥5% BM blasts at diagnosis, because this threshold represents a potential trigger for cytoreductive therapy. Patient cohorts published so far were in general more heterogeneous with regard to BM blast count (< or >5%), International Prognostic Scoring System risk stage, age, or conditioning intensity, thereby impeding a direct comparison. Nevertheless, our results, which were confirmed in a multivariate analysis, support the notion from the previous analyses showing no apparent advantage of pretransplant cytoreduction and comparable outcome after upfront transplantation [14-21]. In addition, OS and RFS in the upfront group did not differ between patients with a BM blast count <10% and those with >10%, thereby challenging a recent recommendation of an international expert panel to perform cytoreduction in patients with BM blasts > 10% [1].

Still, all these retrospective analyses have the same inherent limitations, which need to be taken into account when interpreting their results. Patients treated with CTX and HMAs who finally received an allo-HSCT represent a selected group, because of a relevant dropout rate during cytoreduction. Patients who received CTX but failed to proceed to transplantation because of toxicity, disease progression, or death are excluded from retrospective reports on the outcome of allo-HSCT in MDS and sAML. Indeed, this was recently shown in prospective trials by a day 30 mortality of 13.7% after conventional CTX [9] and also by an unexpectedly high dropout rate of 33% after 4 cycles of Aza before envisaged RIC transplantation [27]. This selection effect because of failure to proceed to transplant may apply to a lesser extent to patients in the upfront group. Still, the dropout rate according to pretransplant treatment can only be compared exactly within a prospective trial, which includes transplant-eligible patients at the time the decision to proceed to allo-HSCT is made before selection of a pretransplant strategy. Another limitation of our and all other retrospective analyses is a potential selection bias resulting in differences regarding patient and disease characteristics in the different treatment groups. We tried to follow a stringent strategy to perform an early upfront transplant primarily depending on donor availability, which is reflected by a comparable time between diagnosis and transplant in the 3 treatment groups. Nevertheless, we cannot exclude that patient- and disease-related factors such as karyotype, disease subtype, and kinetics may have influenced the choice in individual patients. Furthermore, a considerable number of patients were referred to our center for allo-HSCT only after initial therapy had been performed by the referring physicians. As a consequence, some imbalances occurred between the treatment groups in our analysis and likewise in other

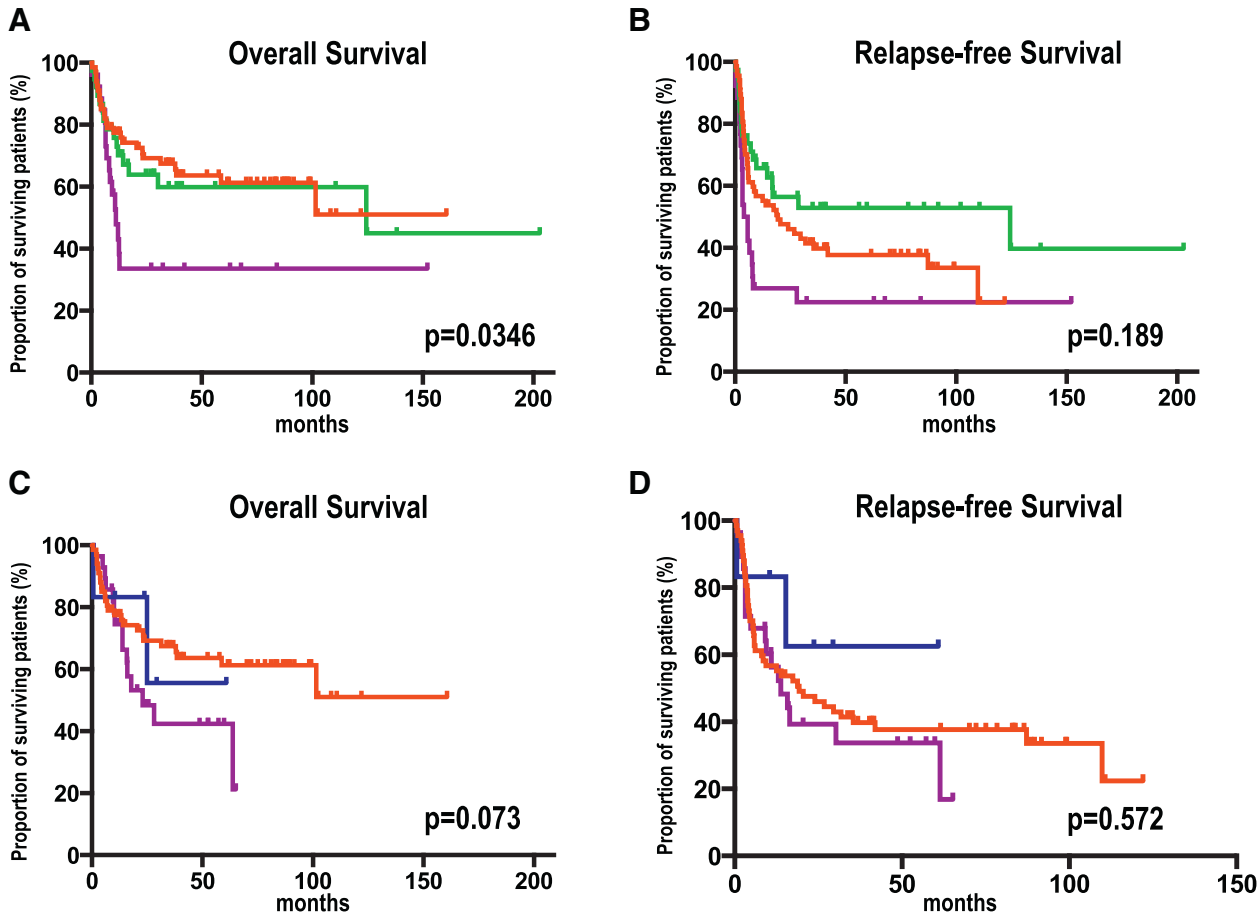

Figure 3. Outcome after allo-HSCT according to remission state. (A and B) OS and RFS for patients in the upfront group (red curve) in comparison with patients who either achieved CR after CTX (green curve) or were refractory (purple curve). (C and D) OS and RFS for patients in the upfront group (red curve) in comparison with patients who either achieved CR after HMA (blue curve) or were refractory (purple curve).

publications. Although patients in the upfront group suffered more often from high-risk features such as therapy-related MDS and chronic myelomonocytic leukemia, there were more patients with sAML in the CTX group. Still, reflecting the aggressive disease phenotype also in the upfront group, over one-third of those patients progressed between diagnosis and allo-HSCT. Patients pretreated with HMA were older and accordingly more often received a RIC regimen. To overcome this limitation of our and all other published reports, a prospective randomized trial is definitively required to finally answer this important clinical question.

In addition to the risk of failure to proceed to transplant, another disadvantage of pretransplant therapy is the relatively low CR rate after conventional CTX and HMAs in MDS. In line with CR rates reported in the literature ranging from 33% to 59% after CTX [4,9,10] and from 7% to 17% after HMAs [6-8,28,29], we observed a CR rate of 59% and 18%, respectively. This implies that when a pretransplant therapy is considered, a careful patient selection weighting the chance to achieve CR and thereby to restore blood cell counts against the risk of treatment-related complications is crucial. For example, patients with complex or monosomal karyotype have a low likelihood to achieve CR after conventional CTX and may therefore be candidates for novel approaches such as CPX-351. This liposomal formulation of daunorubicine and cytarabine has recently proven to induce a higher remission rate and better OS particularly in this patient group [9]. However, on the other hand, CPX-351 has also been shown to induce long-lasting cytopenias, putting patients at risk for infectious complications that may be a burden during allo-HSCT.

Besides the influence of pretransplant therapy, 2 procedure-associated factors that may influence outcome after transplantation are the intensity of the conditioning regimen and donor choice. The issue of conditioning intensity is still controversial even after 2 prospective randomized trials [30,31], which had opposing results. These may be explained by the inclusion of different patient populations, for example different proportions of patients with early MDS (<5% BM blasts) or patients being in remission at transplant. In contrast to these studies, our analysis of a homogenous group of patients with advanced MDS or sAML and high-risk features revealed a positive effect of full-intensity conditioning on OS, RFS, and CIR. This finding argues for an individualized conditioning intensity to be as intensive as possible in an individual patient. Age and comorbidities are the most important factors to guide this strategy. Furthermore, in our analysis the use of an unrelated donor was associated with a higher risk of relapse. This may be linked to the use of high-dose antithymocyte globulin (ATG) in patients with a high risk for relapse, because significantly more patients receiving grafts from unrelated donors received ATG (90% versus 16%, $P < .001$). Although the impact of ATG on the likelihood of relapse is still a matter of debate [32-34], even after several prospective trials in patients with heterogeneous risk factors and disease stages,

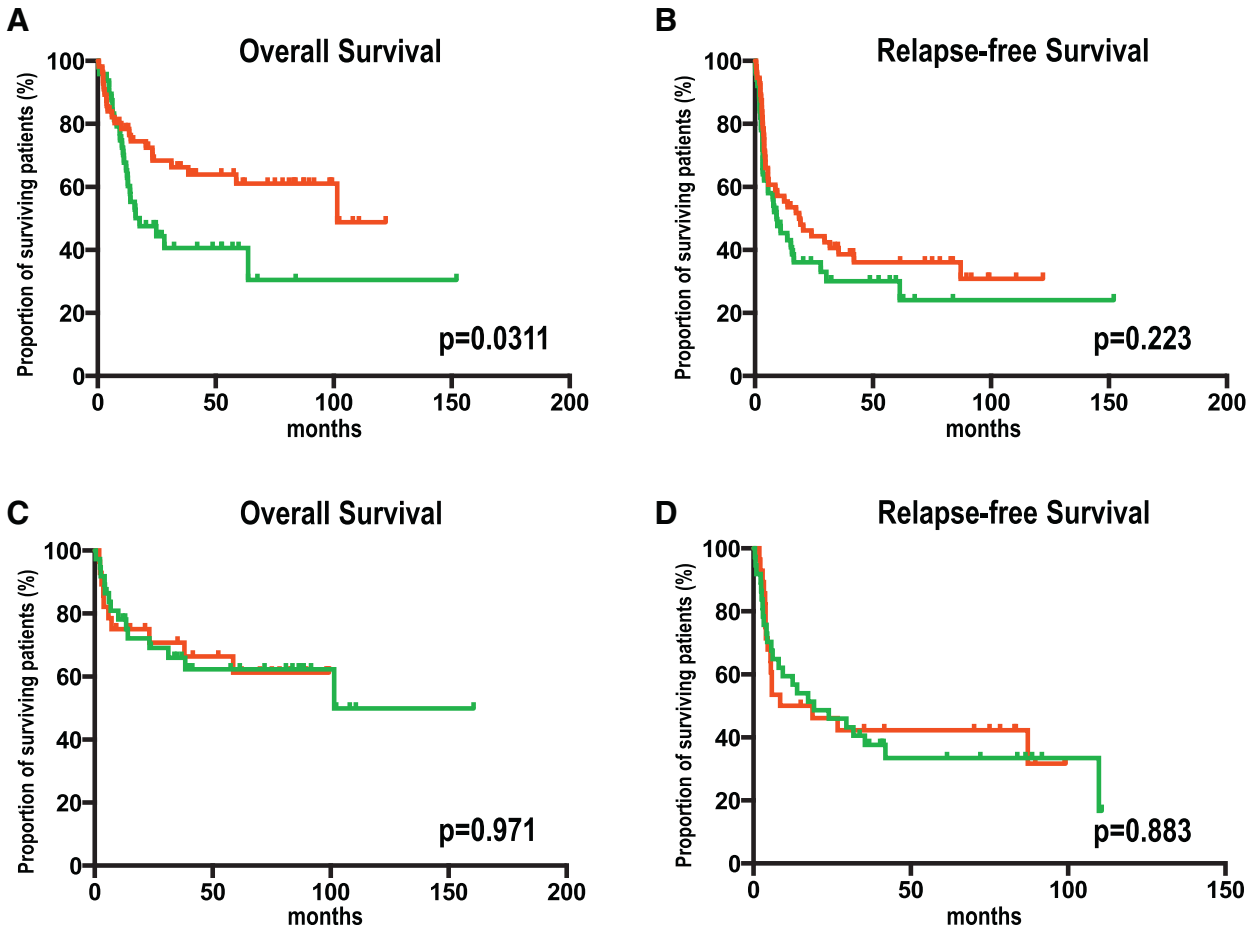

Figure 4. Outcome after allo-HSCT according to disease burden and treatment status. (A and B) OS and RFS for patients with ≥5% BM blasts at the time of transplantation in the upfront group (red curve) in comparison with patients who were pretreated with CTX or HMAs (green curve). (C and D) OS and RFS for patients in the upfront group dichotomized at a cut-off of 10% BM blasts (green curve, <10% BM blasts; red curve, ≥10% blasts).

again our results in a homogenous group of patients with high-risk MDS and sAML suggest a negative effect of high-dose ATG on the likelihood of relapse. Because previous studies have shown a dose effect of ATG in terms of relapse risk, our results underline the importance of a careful consideration of relapse risk and donor characteristics to guide the use and the dosage of ATG.

Finally, we show that patients who did not respond to CTX or HMAs had a lower OS compared with patients receiving an upfront transplant without the attempt of cytoreduction. However, there was no apparent difference regarding RFS between these 2 groups. This suggests on the one hand that the absolute disease burden at the time of allo-HSCT estimated by the percentage of BM blast itself may not be the most relevant factor

Table 3
Univariate Analysis for Relapse Incidence and NRM

	CIR			NRM		
Variable	HR	95% CI	p value	HR	95% CI	p value
IPSS			0.970			0.119
int-2/high vs. low/int-1	0.99	0.51 to 1.9		4.98	0.66 to 37.45	
Cytogenetics			0.175			0.363
abnormal vs. normal	1.43	0.85 to 2.39		1.52	0.62 to 3.73	
Poor-risk cytogenetics			0.044			0.066
yes vs. no	1.68	1.02 to 2.78		2.20	0.95 to 5.1	
Therapy-related			0.170			0.834
yes vs. no	0.61	0.30 to 1.24		1.11	0.41 to 3.02	
Age			0.042			0.413
> 55 years vs. <= 55 years	1.68	1.02 to 2.77		1.43	0.61 to 3.35	
Conditioning			0.018			0.277
standard-dose vs. reduced-intensity	0.51	0.29 to 0.89		0.59	0.23 to 1.52	
Donor			0.001			0.314
related vs. unrelated	0.31	0.15 to 0.64		1.55	0.66 to 3.62	
Type of therapy			0.687			0.551
upfront vs. cytoreduction	1.11	0.68 to 1.80		0.77	0.32 to 1.83	

Table 4
Multivariate Analysis for OS and RFS

	OS			RFS		
Variable	HR	95% CI	p value	HR	95% CI	p value
Poor-risk cytogenetics			0.001			<0.0001
yes vs. no	2,63	1.45 to 3.85		2,18	1.43 to 3.30	
Age			0.340			
>Median	0.75	0.41 to 1.37		–		
Conditioning			0.002			0.004
standard-dose vs. reduced-intensity	0.42	0.23 to 0.75		0.50	0.32 to 0.80	
Donor						0.006
related vs. unrelated	--			0.49	0.29 to 0.82	
Type of therapy						
upfront vs. cytoreduction	1,45	0.76 to 2.77	0.259	1,48	0.83 to 2.65	0.186

SE indicates standard error.

Table 5
Multivariate Analysis for Relapse Incidence and NRM

	CIR			NRM		
Variable	HR	95% CI	p value	HR	95% CI	p value
Cytogenetics			0.030			
abnormal vs. normal	1.789	1.06 to 3.03		–		
Donor			0.002			
related vs. unrelated	0.330	0.16 to 0.64		–		
Conditioning			0.006			
standard-dose vs. reduced-intensity	0.450	0.25 to 0.80		–		
Therapy-related			0.098			
yes vs. no	0.546	0.26 to 1.12		–		
Type of therapy			0.486			
upfront vs. cytoreduction	1.197	0.72 to 1.98		0.767	0.32 to 1.83	0.551
Age						
>Median	--			–		

determining post-transplant outcome. Instead, the prognostic impact of BM blast count at transplant should be interpreted in the context of the type of pretransplant treatment. On the other hand it suggests that more patients in the upfront group could be rescued by salvage therapy after relapse. Indeed, untreated patients had a significantly higher likelihood to respond to salvage therapy with HMAs and donor lymphocyte infusion than patients who had received cytoreductive treatment before transplantation, which then translated into a survival benefit after relapse. Overall, these findings imply that pretransplant therapy may favor the iatrogenic selection of resistant clones, which poorly respond to salvage therapy in case of relapse after allo-HSCT. This concept that pretransplant CTX or HMAs select for resistant myeloid clones has been shown after CTX and autologous transplantation [35-37], and a recent report about sequencing results of 9 relapsed MDS patients suggests that pretransplant HMA therapy may also influence clonal composition and expansion after allo-HSCT [38]. Surprisingly, response to salvage therapy in case of relapse was independent from the response to pretransplant cytoreduction. Therefore, achieving CR before transplant is a prognostic factor for RFS, but once relapse occurs these patients respond less well to salvage treatment.

We finally conclude from our results, with the limitations of retrospective studies discussed, that upfront allo-HSCT in patients with high-risk MDS and sAML, incorporating a sequential FLAMSA-based conditioning regimen, is feasible and may result in similar long-term survival as in patients who receive allo-HSCT in remission after debulking CTX. Upfront allo-HSCT may increase the number of patients eligible for transplant by avoiding some of the substantial risks associated with pretransplant cytoreduction, such as toxicity, progression, and death. We further suggest that the success of the treatment of relapse after allo-HSCT largely depends on pretransplant strategies, as current debulking approaches seem to select for resistant clones. To finally answer the question of an ideal "bridge to transplant," prospective studies incorporating more effective induction therapies including the use of novel agents and comparing them with upfront allo-HSCT are urgently needed.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: G. K., T. S., and U. G. conceived and designed the study. T. S., N. W., M. L., U. G., and G. K. analyzed and interpreted the data analysis. T. S., M. L., U. G., and G. K. wrote the manuscript. All authors provided patient data, collected and assembled data, and approved the final manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2019.03.011.

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