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Hematopoietic Cell Transplantation in Myelodysplastic Syndromes after Treatment with Hypomethylating Agents

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Abstract

The prognosis of patients with myelodysplastic syndromes (MDS) following failure of hypomethylating agent (HMA) therapy is poor. Allogeneic hematopoietic cell transplantation (HCT) can be effective in curing patients who have failed therapy with HMA. However, published results have not addressed the outcomes with HCT in this setting. We identified 125 MDS patients who had been treated with HMA and underwent subsequent HCT. Among these, 68 were considered HMA failures, and 57 responders. Failure was defined as progression to higher grade MDS or acute myeloid leukemia (AML), lack of hematological improvement after at least 4 HMA cycles, or loss of response after initial improvement. Response was defined as showing at least hematological improvement. Outcomes were compared using Cox regression. Overall, 73 of 125 HMA-treated patients (58%) had died by the time of last contact. Median follow-up of survivors, measured from HCT, was 41.9 (range, 2.7–98.5) months. The estimated probability of relapse at 3 years was 56.6% and 34.2% among failing and responding patients, respectively (hazard ratio [HR] 2.1, 95% CI, 1.2–3.66, $p < 0.01$). The estimated probability of relapse-free survival (RFS) at 3 years was 23.8% and 42% in failing and responding patients, respectively (HR for relapse/death 1.88, 95% CI, 1.19–2.95, $p < 0.01$). The risk of non-relapse mortality was similar for both groups (HR 1.12, 95% CI, 0.52–2.39, $p = 0.77$). Failure of treatment with HMA was associated with higher risk of post-HCT relapse than observed in patients responding to HMA. Prospective trials are needed to evaluate the efficacy of novel conditioning regimens and post-HCT maintenance strategies in patients who have failed HMA pre-HCT.

Keywords

MDS; allogeneic transplantation; hypomethylating agents; azacitidine; decitabine

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INTRODUCTION

The hypomethylating agents (HMA) azacitidine (AZA) and 2-deoxy-azacytidine [decitabine (DEC)] have shown clinical activity in myelodysplastic syndromes (MDS) [1, 2]. They are nucleoside analogues with direct cytotoxicity and the ability to interfere within epigenetic regulation processes. Although AZA treatment was associated with overall survival (OS) benefit when compared to conventional care in MDS patients, the median prolongation of survival was on the order of only nine months [3], and in most patients the life expectancy is reduced by more than 90% in comparison to controls. Hematopoietic cell transplantation (HCT) remains the only therapeutic approach with curative potential in this setting [4].

Retrospective analyses have confirmed a very poor prognosis for patients who failed to respond or whose disease progressed on HMA [5, 6]. Salvage options are limited, but include low or higher dose chemotherapy, investigational agents, HCT or supportive care. While HCT may be the treatment associated with the best outcome based on retrospective analyses, only a third of patients with HMA failure experienced prolonged relapse-free survival [5]. While prior studies have evaluated the use of hypomethylating therapy before HCT [7, 8], no studies to date have focused on the population of patients who have failed HMA.

The aim of the current study was to compare post-HCT outcomes among patients who failed HMA to outcomes of patients who responded to HMA prior to HCT, with a focus on the risk of relapse.

PATIENTS AND METHODS

Patients

Between June 2004 (FDA approval of AZA), and December 2013, 125 patients with MDS or chronic myelomonocytic leukemia (CMML) who had been treated with HMA underwent HCT at the Fred Hutchinson Cancer Research Center (Fred Hutch). The diagnosis was confirmed according to World Health Organization (WHO) 2008 criteria [9]. The disease risk was assessed using the international prognostic scoring system (IPSS) [10], as well as the revised IPSS (IPSS-R) [11]. All patients or their legal guardians had given informed consent to use medical information for research purposes as approved by the Institutional Review Board of the FHCRC in accordance with the Declaration of Helsinki.

In addition to the 5-group cytogenetic classification by Schanz et al. [12] that has been incorporated into the IPSS-R, we also identified patients with monosomal karyotype as defined elsewhere [13]. MDS was considered “secondary” if preceded by cytotoxic therapy for hematological or non-hematological disorders.

Definition of HMA Failures and Responders

Response to HMA was determined using the International Working Group (IWG) 2006 criteria [14]. Treatment failure was defined as loss of response after initial improvement, progression to higher risk MDS or AML, or no hematological improvement after at least 4 HMA cycles.

Assessment of Transplant Outcomes

The day of engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) of $0.5 \times 10^9/L$. Primary graft failure was defined as not reaching an ANC of $0.5 \times 10^9/L$ by day 28 (day 55 in case of cord blood HCT). Secondary graft failure was defined as a progressive decline in peripheral neutrophil counts after initial recovery. In addition, donor CD3+ T cells <5% on day 28 or donor T-cell decline to <5% after previous evidence of engraftment were considered evidence of primary or secondary graft failure, respectively [15]. The analyses were performed on days 28, 56, 84, 180 and 365, and then as clinically indicated.

Survival time was the time from HCT until death or date of last contact. Relapse-free survival was the time from HCT until death, relapse, or date of last contact. All patients were scheduled for marrow aspiration and biopsy on day 28, day 84, and 1 year post-HCT with morphology, flow cytometric, and cytogenetic analyses. Relapse was defined as the recurrence of any cytogenetic abnormality or immunophenotypic markers that were present pre-HCT or by a recurrence of dysplasia or increased bone marrow myeloblast count detected by morphology. Acute and chronic graft vs. host disease (GvHD) were diagnosed, graded, and treated as previously described [16, 17]. In patients who died following relapse, relapse was considered the cause of death, regardless of the proximal cause of death. Causes of death were attributed using previously described criteria [18].

Statistical Analysis

Estimates of overall survival (OS) and progression-free survival (PFS) probabilities were obtained using the method of Kaplan and Meier [19]. Probabilities of relapse, non-relapse mortality (NRM), and GvHD were summarized using cumulative incidence estimates [20], where death without relapse was considered a competing risk for relapse, and relapse a competing risk for NRM. Death and relapse without GvHD were considered competing risks for GvHD.

Cox regression models were fit in order to compare the cause-specific hazards of failure between treatment failures and responders for each of the above endpoints. Variables considered for inclusion into each regression model included gender, age at HCT, secondary nature of MDS, IPSS-R, AML evolution, minimal identifiable disease by cytogenetics at HCT [21], conditioning regimen intensity, and presence of monosomal karyotype [22] at diagnosis. No adjustments were made for multiple comparisons.

RESULTS

Patient and Transplant Characteristics

Patient characteristics are summarized in Table 1. Patients who failed HMA were more likely to have a higher stage WHO classification, have evidence of disease at time of HCT, and more likely to have evolved to AML than the patients who did not fail HMA. The median age at HCT was 61 (range, 30–76) years among HMA failures, and 61 (range, 34–77) years in HMA responders. Patients who failed to respond received a median of 5 (range, 1–20) HMA cycles compared to 4 (range, 1–40) cycles in responders. The cytogenetic risk

profiles at diagnosis were similar for failures and responders, as were the proportions of patients with secondary MDS, at 24% and 23%, respectively. A monosomal karyotype [13] was detected in 14 patients who failed to respond (21%) and 17 patients (30%) who responded.

Patients were prepared for HCT with various conditioning regimens, categorized on the basis of treatment components and dose intensities (Table 2). The two cohorts were balanced in regards to regimen intensity, donor, and stem cell source. GvHD prophylaxis consisted of mycophenolate mofetil (MMF) and cyclosporine (CSP) or tacrolimus (TAC) in 68 patients (54%), plus sirolimus in 7 patients (6%); methotrexate (MTX) and CSP or TAC in 40 patients (32%), plus sirolimus in 2 patients (2%); and post-transplant cyclophosphamide with or without CSP or TAC in 8 patients (6%).

HMA Failures and Responders

Among the 125 patients who had received at least one cycle of HMA before HCT, 68 (54%) were classified as HMA failures and 57 (46%) as responders. AZA was given at 75 mg/m²/day for 7 days every 28 days. DEC was administered at 20 mg/m²/day for 5 days every 28 days. Ninety-nine patients (79%) were treated with AZA, 19 patients (15%) with DEC, and 7 patients (6%) received both.

Among the 68 patients who experienced treatment failure, HMA therapy was given as a first-line approach in 64 (94%). Four patients (6%) received HMA as salvage therapy after induction-type chemotherapy. Thirty-one patients who failed first-line HMA were subsequently treated with induction-type chemotherapy before HCT. The decision to initiate induction-type chemotherapy was primarily driven by an increase in bone marrow myeloblast percentage. Among these 31 patients, 26 achieved CR or marrow CR and directly underwent HCT, 5 patients showed no response or disease progression. The other 33 patients who failed first-line HMA went directly to HCT (Figure 1).

Among the 68 patients who experienced treatment failure, 7 (10%) lost the response after initial improvement, 53 (78%) progressed to higher risk MDS or AML, and 8 (12%) had no hematological improvement after at least 4 HMA cycles. Twenty-six of 68 patients (38%) received less than 4 HMA cycles, all of them because of progression to higher risk MDS or AML.

Among 57 responding patients, 4 (7%) had failed to respond to induction-type chemotherapy before HMA. The remaining 53 patients (93%) received HMA as first-line treatment. The best responses to HMA included CR or marrow CR in 44 patients (77%) and PR in 1 patient (2%). Responders included 3 patients (5%) who had progressed to AML before being treated with HMA.

Overall Outcome

Overall, 73 patients (58.4%) had died by the time of last contact, including 46 patients who had relapsed post-HCT. The median time between HCT and relapse was 2.8 (range, 0.2–27.6) months. Twenty-seven patients died from non-relapse causes. Median follow-up from HCT among the 52 survivors was 41.9 (range, 2.7–98.5) months. OS and RFS at 3 years

were 40.8% and 32.1%, and relapse and NRM 46.4% and 21.5%, respectively (Figure 2). Eight patients received a second HCT, 2 for graft failure, and 6 as salvage after relapse.

The estimated probability of grades II-IV (III-IV) acute GvHD was 59.8% (13%). The 3-year estimate of chronic GvHD was 43.1%.

Comparison of HMA Failures and Responders

The estimated probability of relapse at 3 years was 56.6% for HMA failures and 34.2% among responders (Figure 3A). After adjusting for covariates, the risk of relapse was significantly higher among HMA failures (HR 2.1, 95% CI, 1.2–3.66, $p < 0.009$). The estimated probability of RFS at 3 years was 23.8% among HMA failures, and 42% among responders (Figure 3B). The adjusted risk of relapse/death was significantly increased among patients with HMA failure compared to responders (HR 1.88, 95% CI, 1.19–2.95, $p < 0.006$). However, the risk of NRM was similar among HMA failures and responders (HR 1.12, 95% CI, 0.52–2.39, $p = 0.77$). The risk of overall mortality was higher among HMA failures than among responders after adjusting for covariates, but the difference was not statistically significant (HR 1.51, 95% CI, 0.93–2.44, $p = 0.09$). The results of multivariable Cox regression models are summarized in Table 3. Low intensity regimens and monosomal karyotype were associated with a significantly increased risk of death/relapse. Age and monosomal karyotype were associated with a significantly increased risk of death.

DISCUSSION

This analysis showed inferior transplant outcome in patients who failed pre-HCT HMA therapy when compared to HMA responders. Treatment with HMA can induce hematological improvement or remission in a proportion of patients. However, responses are typically of limited duration, and most patients show disease progression within 2 years [3]. Clinical studies show that 40% to 60% of patients do not achieve clinically relevant responses to HMA therapy [3, 23]. Resistance to HMA may depend on biological characteristics of the disease, such as the presence of specific gene mutations, or up-regulation of anti-apoptotic BCL2 family genes [24].

The management of MDS patients who fail to respond to HMA is challenging. Induction chemotherapy as used for AML has been associated with overall response rates (ORR) of 50%–60% [25]. However, the ORR to AML-type chemotherapy appears to be substantially lower when given after HMA failure. Moreover, the risk of treatment-related mortality is a major limitation to the application of AML-type chemotherapy in this setting. Other salvage options include *low-dose* conventional chemotherapeutic agents (e.g. *low-dose* cytarabine, hydroxyurea, mercaptopurine, or melphalan), best supportive care, investigational treatments, and HCT.

Two major studies investigated the results of salvage treatments in patients who failed HMA. The MD Anderson team presented data on 290 patients with low or intermediate-1 risk disease by IPSS [6]. After HMA failure, 83 patients (29%) were treated with cytarabine-based regimens or additional HMA cycles; 91 patients (31%) received investigational compounds; 26 patients (9%) underwent HCT; 90 patients (31%) received best supportive

care only. The ORR was 18% with cytarabine-based therapy, and 16% with investigational compounds. Higher ORR was observed after HCT (69%), but patient selection may have biased outcomes. Overall, the administration of any kind of salvage therapy was associated with improved OS compared to best supportive care, but the gain derived from those strategies tended to be small.

In a French study, information on salvage after HMA failure was available in 270 of 435 high-risk MDS patients (62%) [5]. Among these, 122 received best supportive care, and OS was approximately 4 months. AML-type chemotherapy was given to 35 younger patients or patients with more aggressive disease. Similar to the report by Jabbour et al. [6], the ORR among these 35 patients was 14%, and median OS was 8.9 months. Among 18 patients receiving *low-dose* chemotherapy, none responded, and the median OS was 7 months. Among 44 patients receiving a second attempt with HMA alone or in combination with histone deacetylase (HDAC) inhibitors, single agent thalidomide or its derivatives, or non-registered drugs, the median OS was approximately 13 months. The heterogeneity of this cohort and the mix of treatment strategies renders a comparison to other reports difficult. As indicated before, the 37 patients who received HCT had a median OS of 19.5 months.

HMA have been widely employed as a debulking strategy or maintenance therapy before HCT [7, 8]. Results from prospective clinical trials designed to compare HMA to AML-type chemotherapy before HCT are pending. The present analysis showed that patients who fail to achieve responses to treatment with HMA or progress after initial response to HMA before HCT experience a significantly higher post-HCT incidence of relapse. In contrast, patients who are responding to HMA at time of HCT have a significantly lower rate of relapse. These data should be considered when deciding on the optimal timing of HCT, and patients who are candidates for HCT should be referred early in their treatment course rather than waiting for failure of HMA. Delaying HCT for patients who have responded to HMA may lead to inferior outcomes with HCT if patients progress.

In conclusion, HMA failure is associated with higher risk of relapse after HCT. Additional studies are needed to determine biomarkers associated with response to HMA and develop novel interventions for patients who are likely to have no response to HMA. Both novel conditioning regimens and post-HCT maintenance strategies should be considered for patients who undergo HCT following HMA failure.

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HIGHLIGHTS

- We compared outcomes of 68 MDS patients with HMA failure before HCT with 57 responders
- HMA agents failure was independently associated to worse progression-free survival
- HMA agents failure was associated to a significantly higher 3-year relapse incidence

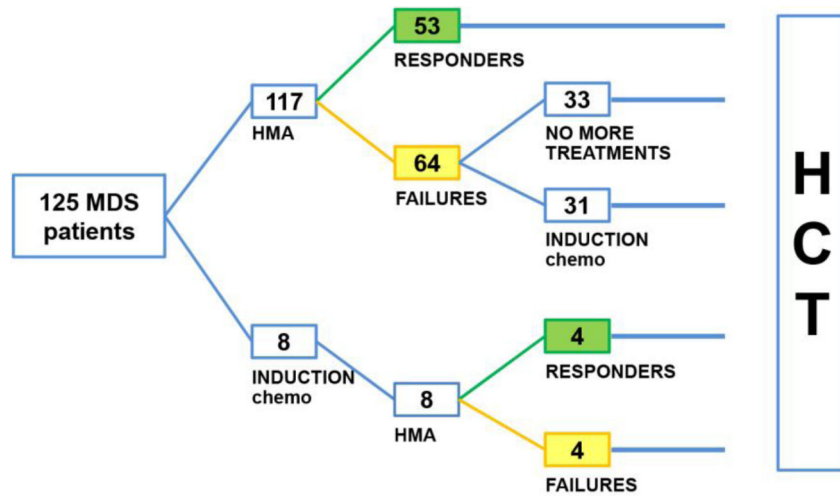


Figure 1.
Pre HCT treatments.

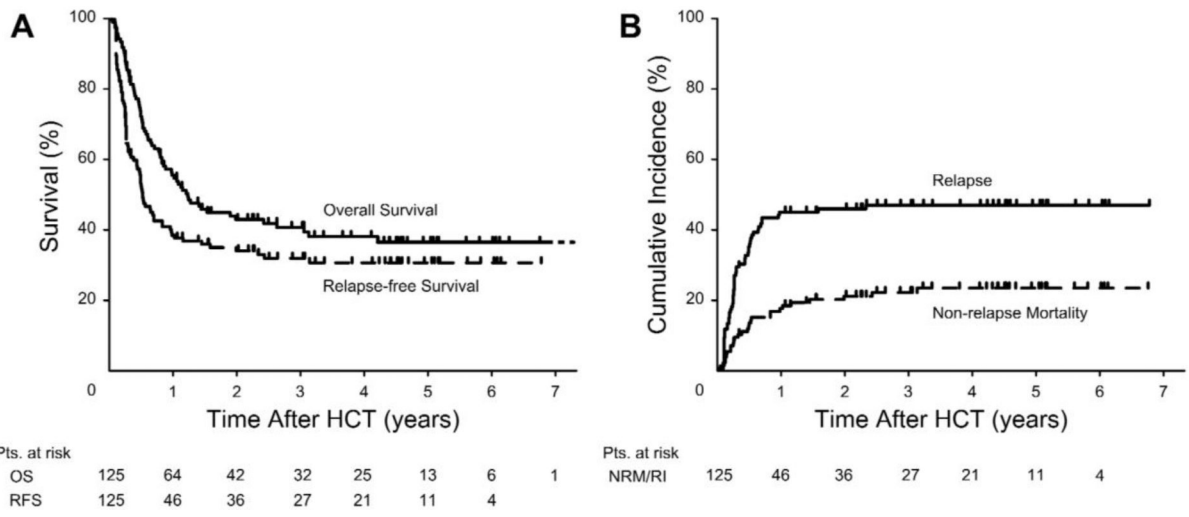


Figure 2.
A) Unadjusted Kaplan-Meier curves for overall survival and relapse-free survival; **B)** cumulative incidence of relapse and non-relapse mortality.

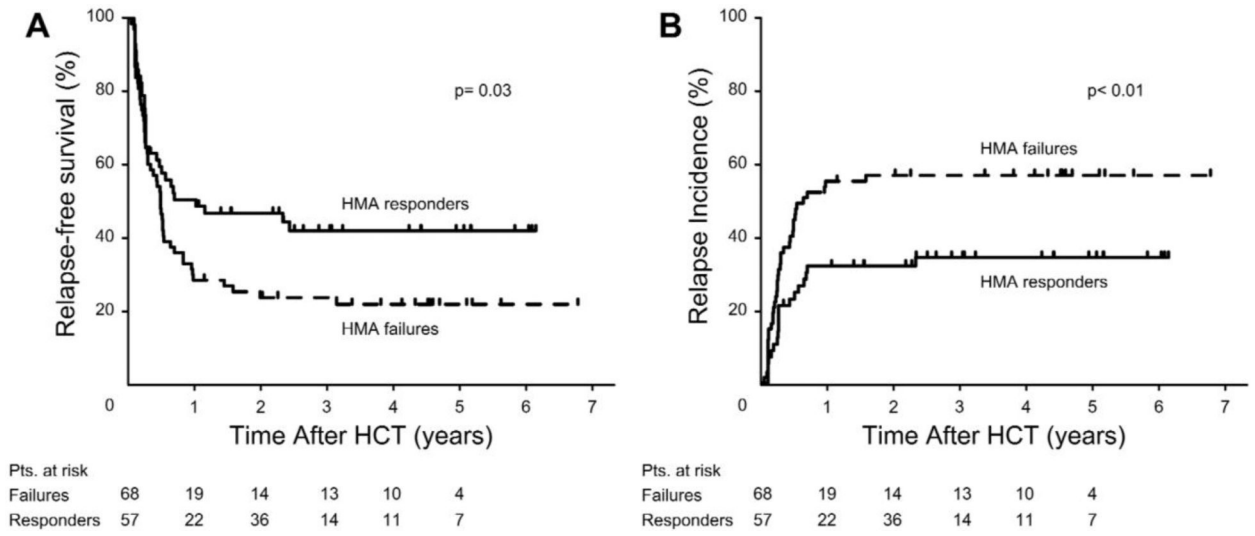


Figure 3.
A) Unadjusted Kaplan-Meier curves for relapse-free survival; **B)** cumulative incidence of relapse.

Table 1.

Patient and Disease Characteristics

Characteristic	Patients	HMA Failures	HMA Responders	P-value
Patients, no. (%)	125	68 (54)	57 (46)	
Male / female, no. (%)	75 (60) / 50 (40)	41 (60) / 27 (40)	34 (60) / 23 (40)	1
Median age at diagnosis, (range), years	60.2 (29.5 – 76.2)	59.8 (29.5 – 74.7)	60.4 (33.3 – 76.2)	0.93
Median age at HCT, (range), years	61.4 (30.4 – 77.2)	61.4 (30.4 – 76.2)	61.4 (33.9 – 77.2)	0.93
Diagnosis, no. (%)				0.017
RCMD	36 (29)	25 (37)	11 (19)	
RARS	2 (2)	2 (3)	-	
Del 5q	1 (1)	1 (1)	-	
MDS-U	8 (6)	1 (1)	7 (12)	
RCUD	9 (7)	3 (4)	6 (11)	
RAEB-1	23 (18)	9 (14)	14 (25)	
RAEB-2	44 (35)	25 (37)	19 (33)	
CMML	2 (2)	2 (3)	-	
Etiology, no. (%)				1
Primary	96 (77)	52 (76)	44 (77)	
Secondary	29 (23)	16 (24)	13 (23)	
Disease duration				0.12
Median time between diagnosis (range) and HCT, months	9.7 (0.8 – 81.8)	11 (0.8 – 66.2)	8.3 (3.2 – 81.8)	
Cytogenetics at diagnosis [12], no. (%)				0.59
Very good and good	58 (46)	34 (50)	24 (42)	
Intermediate	23 (18)	11 (16)	12 (21)	
Poor	14 (11)	7 (10)	7 (12)	
Very poor	28 (22)	14 (21)	14 (25)	
Unknown	2 (2)	2 (3)	0	
IPSS risk at diagnosis, no. (%)				0.6
Low	9 (7)	6 (9)	3 (5)	
Intermediate-1	50 (40)	28 (41)	22 (39)	
Intermediate-2	48 (38)	24 (35)	24 (42)	
High	16 (13)	8 (12)	8 (14)	
Not evaluable *	2 (2)	2 (3)	-	
IPSS-R risk at diagnosis, no. (%)				0.29
Very low	5 (4)	4 (6)	1 (2)	
Low	20 (16)	11 (16)	9 (16)	
Intermediate	29 (23)	16 (24)	13 (23)	
High	42 (34)	25 (37)	17 (30)	
Very high	27 (22)	10 (15)	17 (30)	
Not evaluable *	2 (2)	2 (3)	-	
HMA received, no (%)				0.18

Characteristic	Patients	HMA Failures	HMA Responders	P-value
Azacitidine	99 (79)	58 (85)	41 (72)	
Decitabine	19 (15)	7 (10)	12 (21)	
Both agents	7 (6)	3 (4)	4 (7)	
Disease status at HCT **, no. (%)				<0.001
Complete remission	39 (31)	16 (24)	23 (40)	
Marrow CR	42 (34)	13 (19)	29 (51)	
Partial remission	7 (6)	7 (10)	-	
Stable disease	15 (12)	10 (15)	5 (9)	
Disease progression or relapse	22 (18)	22 (32)	-	
AML evolution before HCT, no. (%)				<0.001
Yes	35 (28)	32 (47)	3 (5)	
No	90 (72)	36 (53)	54 (95)	

* 1 missing cytogenetics, 1 missing peripheral blood cell counts.

** International Working Group 2006 classification [14].

Abbreviations: HMA = hypomethylating agents; HCT = allogeneic hematopoietic cell transplantation; WHO = World Health Organization; RCMD = refractory cytopenia with multilineage dysplasia; RARS = refractory anemia with ring sideroblasts; Del 5q = myelodysplastic syndrome associated with isolated deletion 5q; MDS-U = myelodysplastic syndrome unclassified; RCUD = refractory cytopenia with unilineage dysplasia; RAEB = refractory anemia with excess blasts; CMML = chronic myelomonocytic leukemia; IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System; CR = complete remission; AML = acute myeloid leukemia.

Table 2.

Transplant Characteristics

Characteristic, no. (%)	HMA Failures (N=68)	HMA Responders (N=57)	P value
High intensity conditioning	41	28	0.28
BU 16/CY	18 (26)	8 (14)	
TREO 42/FLU/TBI 2 Gy	7 (10)	10 (18)	
RAB/FLU/TBI 2 Gy	5 (7)	3 (5)	
BU 16/FLU	4 (6)	5 (9)	
RDB/BC8SA/FLU/TBI 2 Gy	3 (4)	2 (4)	
RAB/FLU/TBI 2 Gy/CY	2 (3)	-	
TBI 12–13.2 Gy/CY	1 (1)	-	
RAB/FLU/TBI/LI 14 Gy	1 (1)	-	
Low intensity conditioning	27	29	0.28
FLU/TBI 2–3 Gy	16 (24)	14 (25)	
FLU/TBI 4–4.5 Gy	5 (7)	11 (19)	
CY/FLU/TBI 2–4 Gy	4 (6)	3 (6)	
CLOFA/TBI 2 Gy	2 (3)	-	
BU 8/FLU	-	1 (2)	
Donors			0.61
HLA-matched siblings	18 (26)	19 (33)	
Haploidentical	2 (3)	-	
Matched unrelated	31 (46)	27 (47)	
Mismatched unrelated	10 (15)	6 (11)	
Cord	7 (10)	5 (9)	
Source of stem cells			0.91
Peripheral blood	54 (79)	47 (82)	
Marrow	7 (10)	5 (9)	
Cord	7 (10)	5 (9)	

Abbreviations: BU = busulfan (16 mg/kg or 8 mg/kg); CY = cyclophosphamide; FLU = fludarabine; TREO = treosulfan 42 gm/m²; TBI = total body irradiation; Gy=Gray; RAB = radiolabeled antibodies; RDB = radiolabeled dota-biotin; BC8SA = streptavidin-conjugated antiCD45 antibodies; LI = localized irradiation; CLOFA = clofarabine; HLA = human leukocyte antigen.

Table 3.

Multivariable Cox Regression Models

Variable	Hazard Ratio	95% Lower CI	95% Upper CI	P-Value
RELAPSE INCIDENCE (Observations = 125; Events = 57)				
Group				
<i>HMA Failures</i>	2.10	1.2	3.66	0.009
<i>HMA Responders</i>	1			
Conditioning Regimen				
<i>Low</i>	1.81	1.07	3.06	0.03
<i>High</i>	1			
NON-RELAPSE MORTALITY (Observations = 125; Events = 27)				
Group				
<i>HMA Failures</i>	1.12	0.52	2.39	0.77
<i>HMA Responders</i>	1			
RELAPSE-FREE SURVIVAL (Observations = 124; Events = 83)				
Group				
<i>HMA Failures</i>	1.88	1.19	2.95	0.006
<i>HMA Responders</i>	1			
Conditioning Regimen				
<i>Low</i>	1.67	1.08	2.57	0.02
<i>High</i>	1			
Monosomal Karyotype				
<i>Yes</i>	1.83	1.15	2.93	0.01
<i>No</i>	1			
OVERALL SURVIVAL (Observations = 124; Events = 73)				
Group				
<i>HMA Failures</i>	1.51	0.93	2.44	0.09
<i>HMA Responders</i>	1			
Age at Transplant	1.03	1.01	1.06	0.02
Monosomal Karyotype				
<i>Yes</i>	1.96	1.19	3.24	0.01
<i>No</i>	1			

Abbreviations: HR = hazard ratio; CI = confidence interval; HMA = hypomethylating agents.