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Allogeneic stem cell transplantation in therapy-related acute myeloid leukemia and myelodysplastic syndromes: impact of patient characteristics and timing of transplant

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Abstract

Patients with therapy-related acute myeloid leukemia (t-AML) and myelodysplastic syndromes (t-MDS) have poor survival and high non-relapse mortality (NRM) after allogeneic stem cell transplantation. This retrospective study assessed the transplant outcomes of 29 consecutive patients with t-AML (83%) or t-MDS (17%) treated with allogeneic transplantation. The median age of patients was 51 years. Donors were mostly matched unrelated (52%), and 59% of patients received myeloablative conditioning. Two-year overall survival, event-free survival and relapse incidence were 37%, 34% and 33%; NRM was 17% at 100 days, and 32% at 2 years. Event-free survival was reduced in patients with high-risk cytogenetics ($p = 0.02$), Karnofsky performance status $\leq 80\%$ ($p = 0.001$) and disease after induction $\pm$ consolidation ($p = 0.006$). NRM was higher in patients receiving > 2 therapy lines for previous cancer ($p = 0.01$) and in those allografted > 6 months from diagnosis ($p = 0.03$). In conclusion, allogeneic transplantation should be proposed timely to these patients after an accurate analysis of patient history.

Keywords: Allogeneic stem cell transplantation, therapy-related, acute myeloid leukemia, myelodysplastic syndromes

Introduction

Patients with therapy-related acute myeloid leukemia (t-AML) and myelodysplastic syndromes (t-MDS) have a dismal prognosis [1]. t-AML and t-MDS occur after exposure to chemotherapy and/or radiotherapy for the treatment of solid tumors or hematologic malignancies. Alkylating agent and radiation related t-AML/t-MDS usually occur 5–6 years after exposure [2] and older patients have a higher risk, whereas topoisomerase II inhibitor related t-AML/t-MDS has a shorter latency period (2 years) [1,3]. Cytogenetic abnormalities can be identified in more than 90% of patients with t-AML/t-MDS and usually include deletion of chromosomes 5 and/or 7, 11q23 rearrangement and complex karyotype (≥ 3 cytogenetic abnormalities) [4–7]. Patients affected by t-AML/t-MDS frequently have a poor response to chemotherapy, and their median survival is 7–8 months [5,6]. t-AML has a lower rate of induction remission and a higher risk of relapse than *de novo* AML [8]. Allogeneic stem cell transplantation (alloSCT) can be considered an option for patients with t-AML/t-MDS, but the advantage provided by alloSCT is offset in part by the high non-relapse mortality (NRM) [9]. A large proportion of patients are currently not submitted to alloSCT due to performance status, comorbidities, age or infections, and those receiving alloSCT have a relevant relapse rate and NRM. Since only a small number of patients benefit from transplant, it is critical to understand which patients should undergo alloSCT. This study was aimed at assessing the outcome of alloSCT and which patient characteristics may predict transplant outcomes.

Materials and methods

We reviewed the data of 29 consecutive patients with t-AML/t-MDS who were allografted at four Italian centers between 2000 and 2009. Informed consent was obtained at the time of transplant according to the Declaration of Helsinki. t-AML and t-MDS were defined according to the 2002 World Health Organization classification. Cytogenetic alterations were classified according to the Medical Research Council classification [10]. The criteria of Cheson *et al.* [11]

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were used to define response to therapy. Comorbidities were retrospectively identified and graded according to the Sorror score [12]. Patients were allografted with myeloablative or reduced-intensity conditioning after induction with or without consolidation chemotherapy or as upfront therapy. Donors were human leukocyte antigen (HLA) identical or mismatched siblings, matched unrelated or haploidentical (Table I). Graft-versus-host disease (GVHD) prophylaxis consisted of short-course methotrexate and cyclosporine with or without mycophenolate mofetil. Anti-thymocyte globulin was added to the conditioning regimen in cases of unrelated or mismatched sibling donor. All patients received infection prophylaxis against fungi, bacteria, *Pneumocystis carinii* and cytomegalovirus, as per standard guidelines. Diagnosis and grading of acute and chronic GVHD were assessed by standard criteria [13–15]. Immunosuppression withdrawal followed by donor lymphocyte infusions was allowed for persistent, progressive or relapsed disease in the absence of GVHD.

Statistical methods

Overall survival (OS) was defined as the time from transplant to death from any cause. Event-free survival (EFS) was

Table I. Patient characteristics.

Characteristics	Group	Patients	%/Range
Sex	Male/female	14/15	48%/52%
Age	Median (years)	51	21–67
Previous neoplasia	Hematologic malignancy	23	79%
	Hodgkin lymphoma	15	
	Non-Hodgkin lymphoma	7	
	Acute lymphoblastic leukemia	1	
	Solid tumor	5	18%
	Breast cancer	2	
	Seminoma	1	
	Testis carcinoma	1	
	Osteosarcoma	1	
	Hematologic (Hodgkin lymphoma) and solid tumor (breast cancer)	1	3%
Time from previous neoplasia	Median (months)	86	13–253
Treatment of previous cancer	Chemotherapy	7	24%
	Chemotherapy + radiotherapy	18	62%
	Radiotherapy	4	14%
Previous lines of therapy	<2	14	48%
	≥ 2	15	52%
Previous autologous stem cell transplant	-	7	24%
Diagnosis	t-AML	24	83%
	t-MDS	5	17%
Performance status (Karnofsky)	$>80\%$	19	66%
	$\leq 80\%$	10	34%
Comorbidity score (Sorror)	0	11	38%
	≥ 1	13	45%
	Not available	5	17%
Cytogenetics	Intermediate	8	27%
	High risk	17	59%
	Not available	4	14%
t-AML/t-MDS treatment	Induction ± consolidation + alloSCT	23	79%
	Upfront alloSCT	6	21%
Induction	Idarubicin + cytarabine ± etoposide	12	41%
	Fludarabine + cytarabine ± idarubicin ± GCSF	11	38%
Consolidation	Idarubicin + cytarabine ± etoposide	14	48%
	Fludarabine + cytarabine ± idarubicin	6	21%
Maintenance	Mercaptopurine	3	10%
Response to induction chemotherapy*	CR	16	70%
	PR	6	26%
	PD	1	4%
Pre-transplant disease status	CR1	11	38%
	CR2	1	3%
	PR	4	14%
	PD	7	24%
	Disease at diagnosis	6	21%
Time from diagnosis to alloSCT	Median (months)	5.4	1–25.1
Conditioning	Reduced intensity	12	41%
	Myeloablative	17	59%
Donor	HLA identical sibling	10	34%
	HLA mismatched sibling (allelic mismatch at locus A)	1	3%
	Matched unrelated	15	52%
	Allelic mismatch at 1 locus (B or C)	4	14%
	Allelic mismatch at 2 loci (B and C)	1	3%
	Haploidentical	3	10%

t-AML, therapy-related acute myeloid leukemia; t-MDS, therapy-related myelodysplastic syndrome; alloSCT, allogeneic stem cell transplant; G-CSF, granulocyte-colony stimulating factor; CR, complete remission; PR, partial response; PD, progressive disease; HLA, human leukocyte antigen.
*Percentages calculated for 23 patients who received induction chemotherapy.

Table II. Characteristics, treatments and outcomes of all patients.

No.	Sex/age	Previous neoplasia	Previous treatment	Diagnosis	Karyotype	Induction	Disease status	Donor	Conditioning + T-cell depletion	Best response	aGVHD/ cGVHD	Follow-up
1	F/55	ALL	HD CT	t-MDS	t(7;17), 15q −	FLA	PR	Haplo	Fluda Treo + ATG	CR	Yes/no	Relapse→2nd alloSCT→alive in CR
2	M/46	Testis carcinoma	Surgery + RT	t-AML	+ 8, 9q −	None	Upfront	Identical sibling	Fluda Treo + ATG	CR	Yes/yes	Relapse→death
3	F/40	HL	HD CT + autoSCT	t-MDS	t(7;11)	FLAGIDA	CR1	Unrelated	Fluda Treo + ATG	CR	No/no	Relapse→death
4	F/58	NHL follicular	CT + RT + autoSCT	t-MDS	− 7	None	Upfront	Haplo	Fluda Treo + ATG	CR	Yes/yes	Alive in CR
5	F/35	HL	CT + RT	t-AML	− 7	FLAGIDA	CR1	Identical sibling	Fluda Bus	CR	No/NA	Death by NRM (pneumonia)
6	M/53	Seminoma	CT + RT	t-AML	Normal	FLAGIDA	CR1	Unrelated	Fluda Bus	CR	No/NA	Death by NRM (CMV)
7	F/60	NHL DLBCL	HD CT + autoSCT	t-AML	+ 21	FLA	CR1	Identical sibling	Fluda Bus	CR	No/no	Alive in CR
8	M/63	NHL plasmacytoid	CT + RT	t-MDS	− 7	FLAGIDA	CR1	Mismatched sibling	Fluda Thio Cy + ALEM	CR	Yes/no	Death by NRM (pulmonary *Aspergillus*)
9	M/58	HL	RT	t-AML	5q −	FLAGIDA	PD	Unrelated	Fluda Thio Cy + ATG	CR	No/NA	Death by NRM (EBV)
10	F/66	Breast carcinoma	Surgery + RT	t-AML	Normal	ICE	CR1	Unrelated	Fluda Thio Cy + ATG	CR	No/yes	Alive in CR
11	M/59	NHL small lymphocytic	CT + HD CT + autoSCT	t-AML	Complex	None	Upfront	Identical sibling	Fluda Bus + ALEM	PR	Yes/NA	Relapse→death
12	F/24	HL	HD CT + RT	t-AML	Complex	FLAGIDA	CR1	Unrelated	Fluda Bus	CR	Yes/no	Alive in CR
13	F/53	HL + breast carcinoma	RT (HL); surgery + RT (breast)	t-AML	Complex	IC	CR1	Identical sibling	Fluda Thio Cy	CR	No/yes	Relapse→death
14	F/57	NHL follicular	CT + RT	t-AML	Complex	ICE	PD	Unrelated	Fluda Thio Cy + ATG	CR	Yes/yes	Death by NRM (JCV encephalitis)
15	F/44	HL	CT + RT + HD CT + autoSCT	t-AML	Normal	IC	CR1	Identical sibling	Fluda Thio Cy	CR	Yes/NA	Alive in CR
16	M/40	HL	CT + RT	t-AML	Normal	None	Upfront	Unrelated	Fluda Thio Cy + ATG	CR	Yes/yes	Alive in CR
17	M/38	HL	CT + RT	t-AML	t(8;21),del(9)	FLAIE	PD	Unrelated	Fluda Thio Cy + ATG	CR	Yes/no	Alive in CR
18	M/38	HL	CT + RT	t-AML	Complex	ICE	PD	Unrelated	Fluda Thio Cy + ATG	CR	No/no	Relapse→death
19	M/56	HL	CT + RT + autoSCT	t-AML	Complex	ICE	PR	Haplo	Fluda Thio Cy + ATG	NA	No/no	Death by NRM (sepsis by *Pseudomonas*)
20	F/52	HL	CT + RT	t-AML	Complex	FLAGIDA	PD	Unrelated	Thio Cy + ATG	NA	NA/NA	Death by NRM (heart failure)
21	F/56	HL	CT + RT + HD CT + autoSCT	t-AML	del(6)	IC	PR	Unrelated	Bus Cy + ATG	PR	No/no	Alive with disease
22	F/25	HL	CT + RT	t-AML	NA	None	Upfront	Identical sibling	Bus Cy VP16	CR	Yes/NA	Relapse→death
23	M/39	HL	CT + RT	t-AML	NA	IC	CR2	Unrelated	Thio Cy + ATG	CR	No/NA	Alive in CR
24	M/53	NHL DLBCL	CT + RT	t-AML	del(7)	IC	PR	Identical sibling	Fluda Thio	CR	Yes/yes	Death by NRM (sepsis; MOF)
25	F/47	HL	CT + RT	t-AML	NA	ICE	PD	Identical sibling	Fluda Thio idarubicin	CR	No/no	Relapse→death
26	F/42	Breast carcinoma	Surgery + CT	t-AML	NA	IC	PD	Unrelated	TBI Cy	CR	Yes/Yes	Death by NRM (*Salmonella* B sepsis)
27	M/21	Osteosarcoma	CT	t-AML	t(9;11)	FLAG	CR1	Unrelated	Thio Cy TBI	CR	No/no	Alive in CR
28	M/26	NHL NOS	CT	t-AML	+ 11	ICE	CR1	Unrelated	Bus Mel Cy	CR	Yes/NA	Alive in CR
29	M/29	HL	CT + RT	t-MDS	Complex	None	Upfront	Identical sibling	Fluda TBI 2 Gy	PR	No/no	Relapse→death

M, male; F, female; ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; HD, high-dose; CT, chemotherapy; RT, radiotherapy; autoSCT, autologous stem cell transplant; t-AML, therapy-related acute myeloid leukemia; t-MDS, therapy-related myelodysplastic syndrome; FLA, fludarabine–cytarabine; FLAGIDA, fludarabine, idarubicin, G-CSF; ICE, idarubicin, cytarabine, etoposide; IC, idarubicin, cytarabine; FLAIE, fludarabine, cytarabine, idarubicin, etoposide; FLAG, fludarabine, cytarabine, G-SCF; PR, partial response; CR, complete response; PD, progressive disease; Haplo, haploidentical; Fluda, fludarabine; Treo, treosulfan; ATG, anti-thymocyte globulin; Bus, busulfan; Thio, thiotepa; Cy, cyclophosphamide; ALEM, alemtuzumab; VP16, etoposide; Mel, melphalan; TBI, total body irradiation; alloSCT, allogeneic stem cell transplant; NRM, non-relapse mortality; CMV, cytomegalovirus; aGVHD/cGVHD, acute/chronic graft-versus-host disease; EBV, Epstein–Barr virus; MOF, multi-organ failure.

defined as the time from transplant to progression or relapse or death from any cause. NRM was defined as the probability of dying from any cause other than disease without previous competing events (relapse or progression). OS and EFS were estimated using the Kaplan–Meier method and groups were compared by log-rank test. NRM and relapse incidence were calculated by the cumulative incidence method considering each other as competing events, and groups were compared by Gray test [16]. All tests were two-sided. The analysis was performed using R software, version 2.10.1.

Results

Patient characteristics

Patient characteristics and treatments are shown in Tables I and II. Twenty-nine patients were enrolled: 24 (83%) had t-AML and five (17%) had t-MDS. The median age at transplant was 51 years (range, 21–67); the majority of patients had a previous hematologic malignancy (82%). Previous cancer was treated with chemotherapy (seven patients, 24%), radiotherapy (four, 14%) or both (18, 62%). Fifty-two percent of patients had received >2 therapy lines before the diagnosis of t-AML/t-MDS, which occurred at a median time of 86 months (range, 13–253) after the previous cancer treatment. Cytogenetic analysis was performed in 25 patients (86%), and 17 patients (59%) had high-risk cytogenetics. Twenty-three patients (79%) received induction chemotherapy, which consisted of idarubicin + cytarabine ± etoposide (12 patients, 41%) orfludarabine + cytarabine ± idarubicin ± granulocyte-colony stimulating factor (G-CSF) (11 patients, 38%). Fifteen (65%) of those receiving an induction had an infectious complication during aplasia. Twenty patients received consolidation chemotherapy consisting of idarubicin + cytarabine ± etoposide (14 patients, 48%) or fludarabine + cytarabine ± idarubicin (six patients, 21%), 11 patients received a second consolidation mainly with cytarabine (seven patients, 24%) and three patients received a cytarabine-based third consolidation cycle. Three patients (10%) received maintenance with mercaptopurine. At transplant, 41% of patients were in complete remission (CR), 38% of patients had disease after treatment and 21% of patients were transplanted upfront. Median time from t-AML/t-MDS diagnosis to alloSCT was 5.4 months (range, 0–25). At transplant, 10 patients (34%) had a Karnofsky performance status (PS) $\leq 80\%$. Seventeen patients (59%) received myeloablative conditioning, which was mainly busulfan- or treosulfan-based, whereas 12 patients (41%) received reduced-intensity conditioning with fludarabine–thiotepa–cyclophosphamide or fludarabine–total body irradiation (TBI) 2 Gy.

Response to allogeneic transplant, survival, relapse and non-relapse mortality

The median follow-up of surviving patients was 44 months (median, 2–97 months). Twenty-four patients (83%) achieved CR after allogeneic transplant. The median remission duration was 21 months (range, 2–97 months). Twelve patients (41%) are alive as of last follow-up, and 11 patients (38%) are in CR. Nine patients (31%) relapsed at a median time of 5 months (range, 2–34) after alloSCT. Eight patients (28%) died of disease, and nine (31%) died of NRM at a median time of 3 months (range, 0–20) after alloSCT. The main cause of NRM was infection (eight patients, 29%). One- and 2-year OS

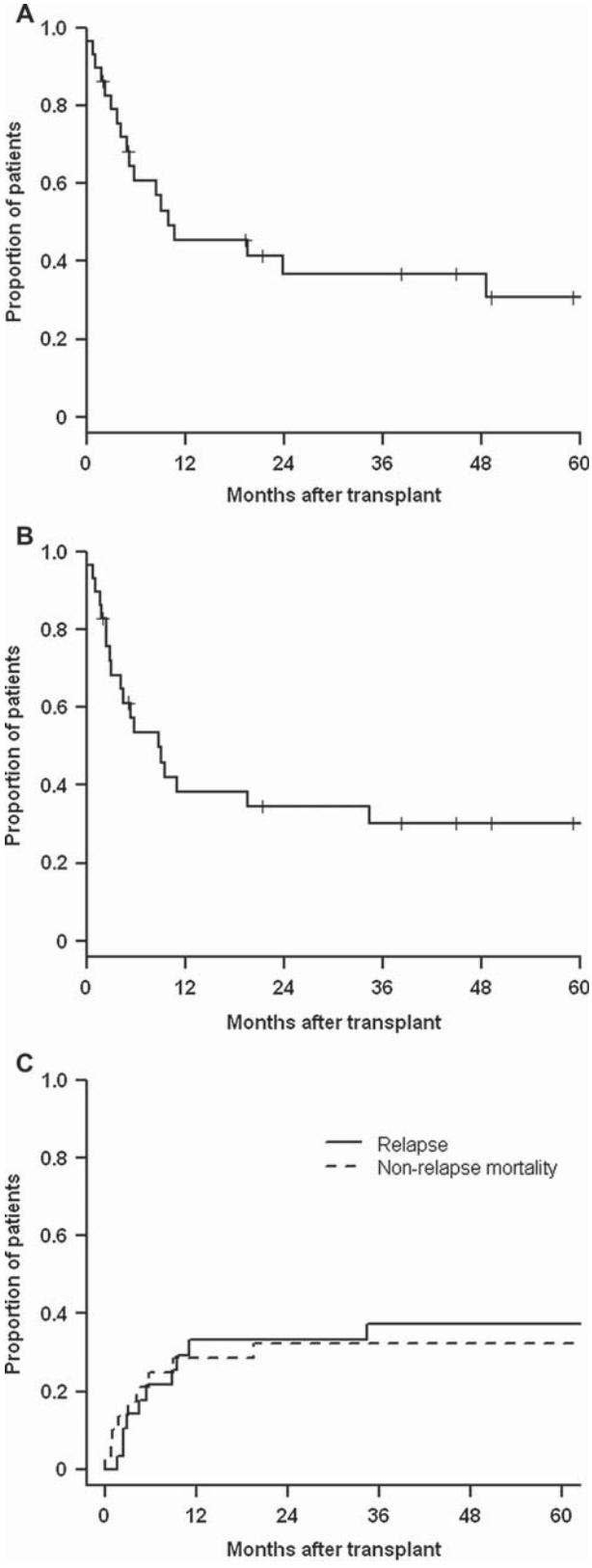

Figure 1. Survival, relapse and non-relapse mortality. (A) Kaplan–Meier analysis of overall survival (all patients, $n = 29$). (B) Kaplan–Meier analysis of event-free survival (all patients, $n = 29$). (C) Incidence of relapse and non-relapse mortality by Cumulative Incidence method with competing risks (all patients, $n = 29$).

was 46% and 37% (median, 9.9 months) [Figure 1(A)], and EFS was 38% and 34% (median, 8.7 months) [Figure 1(B)]. Relapse incidence was 33% at both 1 and 2 years, and NRM was 17% at 100 days, 29% at 1 year and 32% at 2 years [Figure 1(C)]. Fourteen patients (48%) had acute GVHD of any grade after alloSCT; nine (31%) patients had grade ≥ 2 acute GVHD. Eight patients (28%) had chronic GVHD, and three patients (10%) had extensive chronic GVHD. Three patients (10%) received donor lymphocyte infusions at relapse; one of them is alive in CR whereas the other two died of disease.

Analysis of patient characteristics

Overall survival and EFS were reduced in patients with high-risk cytogenetics (high vs. intermediate, $p = 0.04$, and $p = 0.02$, respectively) [Figure 2(A)]. Patients with PS $\leq 80\%$ had a significant reduction of OS ($p = 0.01$) and EFS ($p = 0.001$) [Figure 2(B)]. None of the patients with PS $\leq 80\%$ are event-free as of last follow-up, and only one of them is alive; in contrast, 12 of 20 patients with PS $> 80\%$ are alive and event-free.

Patients with disease after therapy had a worse EFS compared to those in CR or transplanted upfront (2-year EFS 9% for patients with disease at transplant vs. 52% for patients in CR and 50% for patients upfront, $p = 0.006$) [Figure 2(c)]. Similarly, OS was inferior in patients with disease after therapy (2-year OS of 14%) compared to those in CR or transplanted upfront (2-year OS of 52% and 50%, $p = 0.13$).

Patients who received more than two lines of chemotherapy for the previous cancer had a reduced OS ($p = 0.05$) and a trend toward shorter EFS ($p = 0.09$) compared to patients with fewer treatments. The three patients treated with maintenance before alloSCT had shorter OS ($p = 0.007$) and EFS ($p = 0.02$) as compared to patients not receiving maintenance. Non-relapse mortality was reduced in patients receiving alloSCT within 6 months after diagnosis ($p = 0.03$) [Figure 3(A)]: their NRM was 12.5% during the entire follow-up compared to 46% at 1 year and 54% at 2 years for patients allografted more than 6 months after diagnosis. Patients allografted within 6 months after diagnosis numbered 16: eight in CR, four with disease after therapy and four upfront, whereas those having alloSCT more than 6 months after diagnosis more frequently had disease: four in CR vs. seven with disease after therapy vs. two upfront. However, the different distribution of remission status was not statistically significant ($p = 0.39$). Patients in CR transplanted within 6 months had a NRM of 12.5% at 100 days and 1 and 2 years, whereas those transplanted thereafter had a NRM of 25% at 100 days and 50% at 1 and 2 years of follow-up. Patients who received more than two lines of therapy for the previous cancer had a NRM of 60% at 1 year after alloSCT compared to 22% for the other patients ($p = 0.01$) [Figure 3(B)]. Patients receiving maintenance before alloSCT had a higher incidence of NRM (two of three patients died before 6 months after transplant) than other patients ($p = 0.003$). Patients with infectious complications after induction had a trend toward increased NRM ($p = 0.07$), as 53% of them were dead from NRM at 1 year compared to 0% of those without infections. Likewise, patients receiving consolidation had high NRM (42% at 1-year vs. 0% for other patients), although this result did not reach statistical significance ($p = 0.15$). Conditioning regimen (reduced

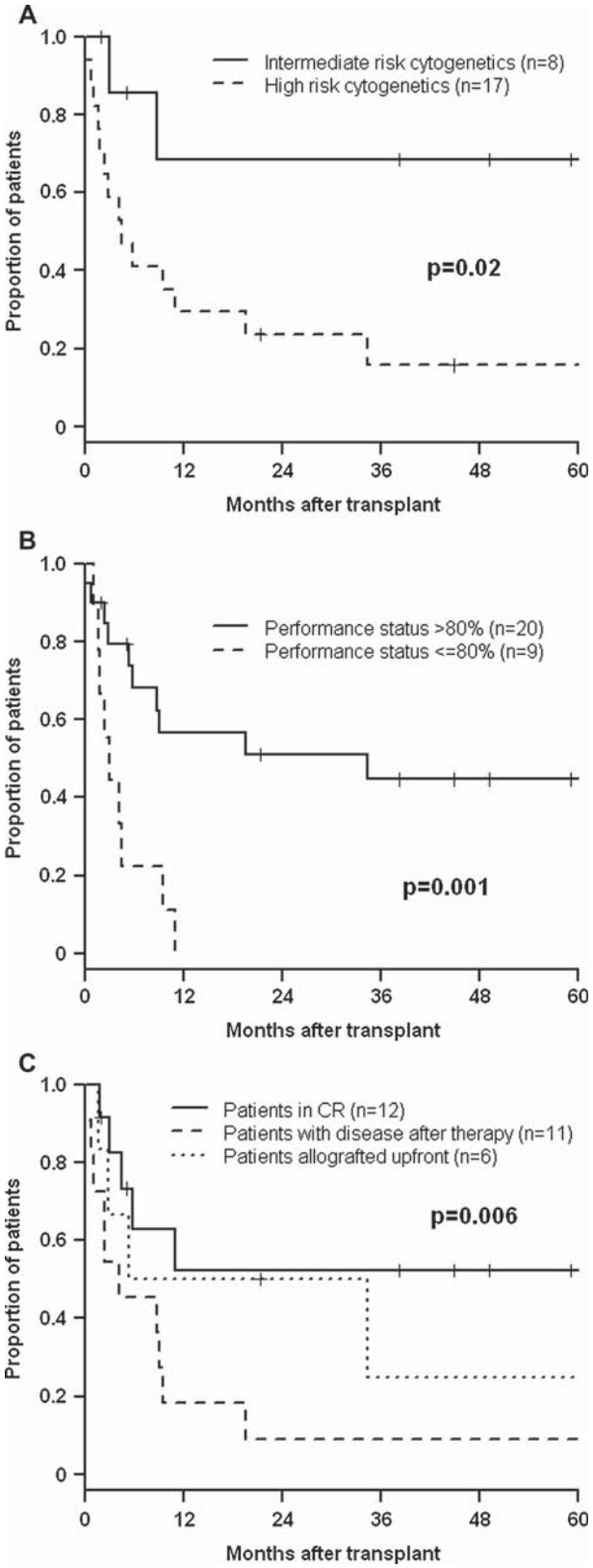

Figure 2. Event-free survival by cytogenetics, Karnofsky performance status and remission status at transplant. (A) Comparison of event-free survival (log-rank test, Kaplan–Meier curves) of patients with intermediate- vs. high-risk cytogenetics (all patients with evaluable cytogenetics, $n = 25$). (B) Comparison of event-free survival (log-rank test, Kaplan–Meier curves) of patients with Karnofsky performance status $> 80\%$ vs. $\leq 80\%$ at transplant (all patients, $n = 29$). (C) Comparison of event-free survival (log-rank test, Kaplan–Meier curves) of patients with disease status at transplant in CR vs. disease after therapy vs. upfront transplant (all patients, $n = 29$).

intensity vs. myeloablative), previous autologous transplant, donor type (sibling vs. unrelated vs. haploidentical), upfront alloSCT and time from previous cancer treatment (>5 vs. ≤5 years) did not significantly impact transplant outcomes. Both acute and chronic GVHD did not have a significant impact on OS ($p = 0.54$ and $p = 0.80$, respectively), EFS ($p = 0.64$ and $p = 0.67$, respectively) or NRM ($p = 0.72$, $p = 0.34$).

Discussion

In this retrospective study we report the results of the analysis of 29 consecutive patients affected by t-AML/t-MDS and treated with allogeneic transplant. With a 2-year EFS and OS of 34% and 37%, our results are consistent with the European Group for Blood and Marrow Transplantation (EBMT) studies, which reported a 3-year EFS of 33%, an OS of 35% and a disease-free survival of 35% in patients with t-AML/t-MDS [17,18].

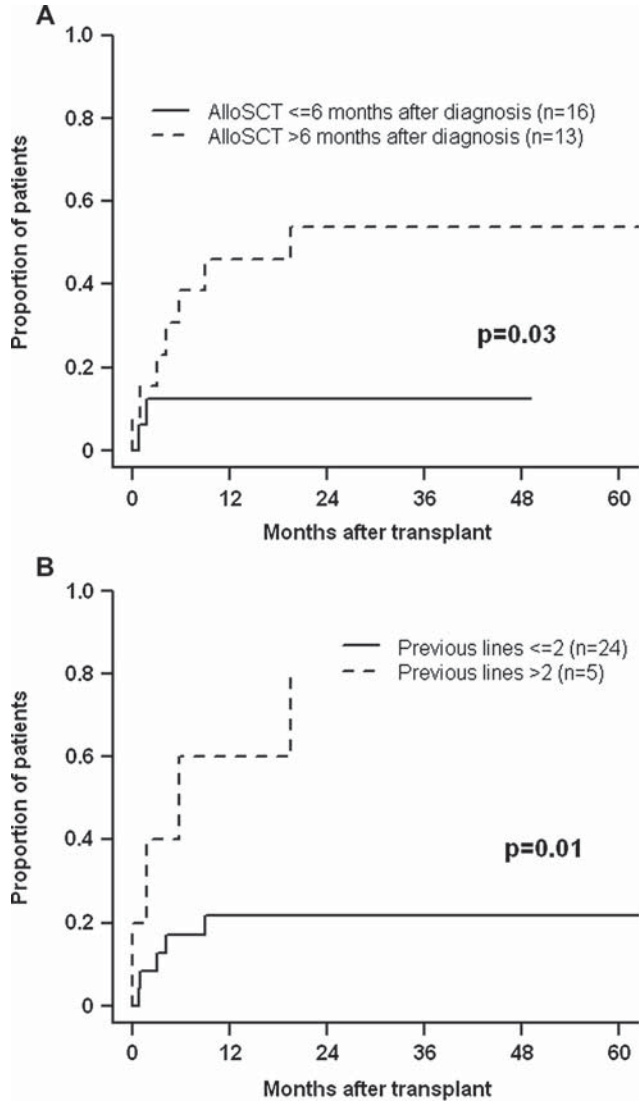

Figure 3. Cumulative incidence of non-relapse mortality by treatment history. (A) Incidence of non-relapse mortality (Cumulative Incidence method with competing risks, Gray test) comparing patients transplanted within 6 months vs. patients transplanted after 6 months after diagnosis of t-AML/t-MDS (all patients, $n = 29$). (B) Incidence of non-relapse mortality (Cumulative Incidence method with competing risks, Gray test) comparing patients receiving ≤2 lines of therapy vs. patients receiving >2 lines of therapy before diagnosis of t-AML/t-MDS (all patients, $n = 29$).

Karnofksy performance status significantly impacted OS and EFS in our series; we did not observe significant effects on NRM probably because of the limited number of events. Sorror *et al.* [12] showed a significant impact of PS on survival and NRM in a heterogeneous cohort of patients mainly affected by AML. A large study showed a significant impact of PS in predicting NRM; however, the cut-off value was higher than in our study (90 vs. 80%) [9]. The differences in survival due to PS may be explained by the fact that transplant toxicity may be increased in fragile patients. Moreover, patients with a low PS are less frequently treated with intensive chemotherapy; as a consequence, their chance to maintain remission is lower. None of our patients with a PS ≤ 80% survived more than 2 years, and they relapsed more often than patients with a high PS (trend, $p = 0.09$). These results demand a careful assessment of PS before alloSCT to select eligible patients.

Our study confirmed the role of cytogenetics in predicting prognosis in patients with t-AML/t-MDS. We showed that patients with t-AML/t-MDS mostly have high-risk or intermediate cytogenetics, and that patients with high-risk cytogenetics have worse survival outcomes, confirming the results reported by other studies [17,19–21]. We also observed that patients in CR fared better than those with disease at transplant, confirming the results of large studies showing a worse survival for patients with high-risk AML not achieving CR after induction therapy [22].

In our cohort, the NRM was 32% at 2 years, which is similar to the results reported by Kröger *et al.* [17] (32% at 1 year and 37% at 3 years) and lower than those of Litzow *et al.* (41% at 1 year and 48% at 5 years) [9]. Probably we found these NRM rates because our patients were allografted in a more recent period than in registry studies. Kröger *et al.* [17] reported that patients allografted after 1998 had a 30% NRM compared to 45% of those allografted before ($p = 0.001$). Litzow *et al.* [9] did not observe differences due to the transplant era, but patients were allografted in a narrower time span. The more recent period may also explain why most of our patients did not receive classic myeloablative conditioning, but received either reduced-toxicity myeloablative or reduced-intensity conditioning. A recent report by the M. D. Anderson group showed a very low NRM in older patients treated with reduced-toxicity conditioning [23]. Actually, the choice of these regimens may rely on the fact that our patients were more than 10 years older (51 vs. 40 years) than patients in registry studies [9,17], and may also explain why, different from those studies, in our study age did not impact survival and NRM.

We report for the first time that a high number (>2) of lines of therapy for the previous cancer can increase NRM. Probably, multiple therapy lines increase organ damage and the incidence of neutropenia, infection events and the immunosuppressive state of the patient. The number of previous therapies has never been assessed in prior studies, in particular registry studies [9,17], in which a detailed treatment history is usually not available.

Patients receiving alloSCT more than 6 months after diagnosis had a worse NRM. In particular, patients achieving CR had more NRM when transplanted more than 6 months after diagnosis compared with those allografted before (50%

vs. 12.5%). Transplant delay may be due to an unsatisfactory response to induction requiring more therapy, infections after induction or consolidation, therapy-related complications and donor availability. We observed that patients receiving consolidation had a trend toward high NRM (53% after 1 year); probably, consolidation adds further organ damage and infection risk. One study reported that consolidation after remission has no impact on transplant outcomes [24]; however, patients with t-AML were not analyzed, and our patients did not all reach CR after induction. Probably, consolidation could be avoided in patients in CR with an available donor, as it adds chances of NRM. Furthermore, maintenance therapy before alloSCT was associated with a high incidence of NRM, but the value of this result is limited because of the low number of patients receiving maintenance. Taken all together, our results suggest that moving forward with transplant as quickly as possible after CR achieves superior outcomes. We also observed that patients developing an infection after induction had a trend toward an increased NRM. Previous infections could facilitate infections after transplant, which are a known cause of NRM owing to immunosuppressants, GVHD and steroid treatment. Patients with high-risk AML frequently have infectious complications after alloSCT, especially unrelated donor recipients like most of our patients [25]. Our patients developing infections after induction had a less than 50% chance of remaining alive after transplant, and thus this factor should be considered when planning alloSCT.

In conclusion, this study confirmed that patients affected by t-AML/t-MDS undergoing alloSCT have a poor prognosis. NRM and relapse equally contributed to death after transplant. Assessment of patient history should be carefully done before proposing allogeneic transplant, and transplant should be performed timely to grant these patients the lowest toxicity, giving them a chance of cure.

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