original article

No improvement of survival with reduced- versus high-intensity conditioning for allogeneic stem cell transplants in Ewing tumor patients

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Background: Outcomes of Ewing tumor (ET) patients treated with allogeneic stem cell

transplantation (allo-SCT) were compared regarding the use of reduced-intensity conditioning (RIC) and high-intensity conditioning (HIC) regimens as well as human leukocyte antigen (HLA)-matched and HLA-mismatched grafts.

Patients and methods: We retrospectively analyzed data of 87 ET patients from the European Group for Blood and Marrow Transplantation, Pediatric Registry for Stem Cell Transplantations, Asia Pacific Blood and Marrow Transplantation and MetaEICESS registries treated with allo-SCT. Fifty patients received RIC (group A) and 37 patients received HIC (group B). Twenty-four patients received HLA-mismatched grafts and 63 received HLA-matched grafts.

Results: Median overall survival was 7.9 months [$\pm$1.24, 95% confidence interval (CI) 5.44–10.31] for group A and 4.4 months ($\pm$1.06, 95% CI 2.29–6.43) for group B patients ($P = 1.3$). Death of complications (DOC) occurred in 4 of 50 (0.08) and death of disease (DOD) in 33 of 50 (0.66) group A and in 16 of 37 (0.43) and 17 of 37 (0.46) group B patients, respectively. DOC incidence was decreased ($P < 0.01$) and DOD/relapse increased ($P < 0.01$) in group A compared with group B. HLA mismatch was not generally associated with graft-versus-Ewing tumor effect (GvETE).

Conclusions: There was no improvement of survival with RIC compared with HIC due to increased DOD/relapse incidence after RIC despite less DOC incidence. This implicates general absence of a clinically relevant GvETE with current protocols.

Key words: advanced-stage Ewing tumor, allogeneic stem cell transplantation, graft versus tumor effect, haploidentical stem cell transplantation, reduced/high-intensity conditioning chemotherapy

introduction

Ewing tumors (ET) constitute a cancer entity of highly malignant, small, round blue cell tumors with features of neuroectodermal or endothelial differentiation [1–5]. They are defined by the expression of a chimeric transcript, commonly deriving from the reciprocal translocation t(11;22)(q24;q12) that results in formation of an EWS/ETS fusion gene, whose detection permits a specific molecular genetic diagnosis [6, 7]. The incidence is 3.3 per million in the Western hemisphere with a peak incidence at the age of 15 years [8]. The most frequent localization of disease onset is bone tissue, preferentially long bones and pelvis. Rarely, soft tissue may harbor the primary tumor site [2]. Metastatic potential is high; approximately 75% of patients present with local disease at the time of diagnosis, whereas the remaining 25% initially present with metastatic disease. Radical surgery alone results in metastatic relapse in the majority of cases, suggesting occult metastases at diagnosis even in apparently localized disease. Despite the impressive improvement of treatment in the last decades using multimodal approaches, 5-year overall survival (OS) of ET patients with localized disease remains at 70%, dropping down to <15% in patients with multifocal primary disease or with early relapse in most studies. Use of involved compartment irradiation and systemic high-dose therapy, both with stem cell rescue, may increase long-term cure rates. However, additional improvements of survival are warranted [9–14].

The existence of a clinically relevant graft-versus-tumor effect in patients with ET after allogeneic stem cell transplantation (allo-SCT) has been a matter of debate [15–17]. Evidence for a graft-versus-Ewing tumor effect (GvETE) could solely be deduced from case reports [18–21]. Allo-SCT following high-intensity conditioning (HIC) or even reduced-intensity conditioning (RIC) regimens has thus remained a merely experimental therapy option in advanced-stage Ewing tumor (AET) patients and a consensus about eligibility criteria is lacking. In order to clarify this issue, we carried out a retrospective European Group for Blood and Marrow Transplantation (EBMT), Pediatric Registry for Stem Cell

Transplantations (PRST), Asia Pacific Blood and Marrow Transplantation (APBMT) and MetaEICESS registries based analysis of 87 ET patients who had either received RIC or HIC before either human leukocyte antigen (HLA)-mismatched or HLA-matched allo-SCT.

patients and methods

study design and data provenience

We collected and evaluated data of 87 patients who were diagnosed with ET from 1984 to 2010 from the EBMT ($n = 69$), APBMT ($n = 5$), PRST ($n = 18$) and MetaEICESS ($n = 4$) registries. Some patients were listed in more than one registry. Inclusion criterion was diagnosis of Ewing sarcoma family of tumors. Diagnosis was based on histopathological examination and in recently diagnosed patients confirmed by molecular genetic detection of ET-specific translocations. In the following sections, patient numbers are followed by specification of respective proportions given in brackets when appropriate, except when data were unavailable.

definitions

Engraftment was defined as an absolute neutrophil count $\geq 0.5 \times 10^9$/l after allo-SCT. In case, patients died within ≤ 100 days after allo-SCT or when information was unavailable, chronic graft versus host disease (cGvHD) was considered as not assessable. Death of complications (DOC) constituted any kind of treatment-related death occurring after allo-SCT in the absence of disease evidence, including engraftment failure. In contrast, the definition of death of disease (DOD) comprised any death directly related to either disease progression or relapse. Progressive disease (PD) was defined as $\geq 50\%$ progression of tumor volume; stable disease (SD) included <50% progression, partial remission (PR) as $\geq 50\%$ reduction and complete remission (CR) as absence of detectable disease. Residual disease (RD) included both PD and PR. Relapse-free survival (RFS) was defined as the time period from the last allo-SCT until the occurrence of any local or metastatic ET evidence in patients who had reached CR after treatment. Early relapse was defined as relapse occurrence ≤ 24 months after diagnosis as opposed to the definition of late relapse (≥ 24 months after diagnosis). Multifocal disease was defined as three or more involved bone sites and/or bone marrow (BM) involvement at diagnosis. Secondary malignancy was defined as any occurrence of post-allo-SCT malignancies other than ET.

HLA mismatch was defined as one or more allele mismatch in HLA class 1 and/or HLA class 2.

patients

The study population consisted of 49 (0.56) male and 38 (0.44) female patients. Median age at allo-SCT was 17 years (range 3–49 years). Depending on the used conditioning regimen before allo-SCT, all patients were assigned either to group A (RIC) or to group B (HIC). Group A comprised 50 of 87 (0.57) and group B 37 of 87 (0.43) patients. In total, 63 of 87 (0.72) patients received grafts from either HLA-matched related or HLA-matched unrelated donors, whereas 24 of 87 (0.28) patients received either haploidentical or otherwise HLA-mismatched grafts. Eligibility for allo-SCT was decided upon the following criteria: local and/or metastatic relapse ($n = 27$), multifocal primary with/without RD ($n = 46$) and autograft mobilization failure ($n = 1$). After induction and conditioning treatment, 42 of 87 (0.48) patients were transplanted in CR, 29 (0.33) in PR and 14 (0.16) in PD. Graft source was only BM in 33 (0.38) patients, only peripheral blood (PB) in 48 (0.55), BM and PB in 2 (0.02) patients and only cord blood in 1 (0.01) patient. Thirty-four (0.39) patients had received autologous grafts, 1 (0.01) patient had received allogeneic graft and 45 (0.52) patients had not received any other graft before allo-SCT. In group A, 4 (0.08) patients were transplanted before the year 2000 and 46 (0.92) in 2000 or later, whereas in group B, 29 (0.78) patients were transplanted <2000 and 8 (0.22) ≥2000. The database contained some previously published patient data [18, 20]. Age and stage distribution did not differ significantly between both groups. Precise patient data of both groups are given in Table 1. All patients or their guardians signed informed consent before therapy. Treatment application relied upon institutional review board approvals according to the precepts established by the Helsinki Conference Declaration.

conditioning regimens and graft versus host disease prophylaxis

RIC regimens were mainly based on the use of fludarabine (60–210 mg/m^2; $n = 47$), alone or in combination with either/or the following drugs: melphalan (MEL; 70–150 mg/m^2; $n = 15$), busulfan (BU; 3–12 mg/kg; $n = 13$), thiotepa (TT; 5–10 mg/kg; $n = 26$), cyclophosphamide (CYC; 30–120 mg/kg; $n = 14$), treosulfan (TREO; 36 or 42 mg/m^2; $n = 2$), topotecan (6 mg/m^2; $n = 3$), carmustine (320 mg/m^2; $n = 1$) or etoposide (ETO; dosage unavailable; $n = 1$) or other nonspecified drugs in nonmyeloablative doses ($n = 1$) with or without the application of 2–4 Gy total body irradiation (TBI; $n = 5$). Furthermore, in some RIC patients, treatment comprised the application of antithymocyte globuline (ATG; $n = 13$), muromonab-CD3 (OKT3; $n = 8$) and/or alemtuzumab ($n = 1$). HIC regimens were mainly based on the use of TBI (10–14 Gy; $n = 23$) in combination with either/or the following drugs: MEL (120–210 mg/m^2; $n = 25$), BU (8–16 mg/kg; $n = 9$), ETO (800–2100 mg/m^2; $n = 18$), carboplatin (800–1500 mg/m^2; $n = 9$), CYC (45–150 mg/kg; $n = 7$), TT (600 or 3300 mg/m^2; $n = 3$), TREO (42 mg/m^2; $n = 2$), vincristine (2 or 2.5 mg/m^2; $n = 2$) or other nonspecified drugs in myeloablative doses ($n = 1$). At least one group B patient received additional ATG. For assessment of conditioning regimens, only the effect of the latest allo-SCT was analyzed even when some patients had received auto- or allografts before. Graft versus host disease (GvHD) prophylaxis included methotrexate, mycophenolat-mofetil, cyclosporine A and/or prednisolone. Individual regimens are provided in the supplemental Tables S1 and S2 (available at *Annals of Oncology* online).

statistical analysis

End points were assessed upon the date of last patient contact. Final database update was conducted in June 2010. Statistical analyses were carried out using R 2.11.0 (The R Foundation for Statistical Computing,

Vienna, Austria) and the PASW Statistics v18.0 (SPSS Inc, Chicago, IL) software. Time values for DOC and relapse/DOD estimates were assessed starting on the date of the last allo-SCT until last follow-up (FU) and for OS, until FU and/or until the occurring event was death independent of the cause. In multivariate analyses, considered variables were patient age, sex, disease status and conditioning regimen for allo-SCT. Hazard ratios, standard errors and confidence intervals (CI) are given when appropriate.

For calculation of OS probabilities, the Kaplan–Meier estimate was used. OS curves were compared using the two-tailed log-rank test. Associations of patient characteristics and conditioning regimens with OS were evaluated in multivariate analyses using Cox proportional hazards.

Cumulative incidence curves were applied to estimate the occurrence of relapse/DOD and DOC, with DOC being a competing event for relapse/DOD and vice versa. For comparison of relapse/DOD incidence between HLA-matched and HLA-mismatched patients, DOC was the competing event. When DOD/relapse and DOC were competing events, uni- and multivariate risk analyses were conducted using the cmprsk and the crr-addson packages designed for R, as proposed by Scrucca et al. [22, 23]. In uni- and multivariate analyses, probabilities of relapse/DOD or DOC for potential explanatory variables were compared using Gray's test or Wald test, respectively. A *P* value <0.05 was considered statistically significant.

results

engraftment and GvHD

Seventy-nine (0.91) patients engrafted successfully, whereas 7 (0.08) patients failed to engraft and for 1 patient, engraftment data were not available. Overall, acute graft versus host disease (aGvHD) was reported in 39 (0.45) patients and absent in 44 (0.51). Overall, cGvHD occurred in 12 (0.14) patients, was absent in 31 (0.36) patients and was not assessable due to either death/last FU before day 100 after allo-SCT in 37 (0.42) patients or to otherwise unavailable information in 7 (0.08) patients. Within group A, 15 (0.30) patients presented with limited and 10 (0.20) with extensive aGvHD, whereas 24 (0.48) patients did not develop aGvHD. Four (0.08) group A patients developed limited, 3 (0.06) developed extensive and 17 (0.34) did not have cGvHD. Status information remained unavailable in 26 (0.52) group A patients due to early death or last FU before day 100 after allo-SCT. Within group B, eight (0.22) patients developed limited and six (0.16) developed extensive aGvHD. In 20 (0.54) group B patients, aGvHD was not detectable. Limited cGvHD was present in three (0.08) and extensive cGvHD in two (0.05) further patients. Status information remained unavailable in 18 (0.49) group B patients due to early death or last FU before day 100 after allo-SCT. An overview is given in Table 2.

overall survival

The 5-year OS estimate for groups A and B was 0.15 ($\pm$0.07) and 0.10 ($\pm$0.05), respectively. OS time did not differ significantly between both groups (Figure 1; log rank *P* = 0.133). At the time of data censure, 37 of 50 (0.74) group A and 33 of 37 (0.89) group B patients had died due to disease or due to complications. Thirteen (0.26) group A and four (0.11) group B patients were alive in CR except for one group A patient who had SD. Median OS was 7.9 months ($\pm$1.24; 95% CI 5.44–10.31) for group A and 4.4 months ($\pm$1.06; 95% CI

Table 1. Patient characteristics

Parameter	Group A (RIC, $n = 50$)		Group B (HIC, $n = 37$)	
	Number	Fraction	Number	Fraction
Median age at diagnosis	15		15	
Range	4–49		2–40	
≤15 years	30	0.60	21	0.57
>15 years	20	0.40	16	0.43
Median age at allo-SCT	17		16	
Range	7–49		3–41	
≤15 years	19	0.38	20	0.54
>15 years	31	0.62	19	0.51
Gender				
Male	28		21	
Female	22		16	
Period of diagnosis				
<2000	11	0.22	28	0.76
≥2000	39	0.78	9	0.24
Period of allo-SCT				
<2000	4	0.08	25	0.68
≥2000	46	0.92	12	0.32
Risk profile leading to allo-SCT				
Early relapse[a]	7	0.14	5	0.14
Late relapse[a]	11	0.22	4	0.11
Multifocal primary and/or residual disease	29	0.58	17	0.46
Autograft mobilization failure	0	0.00	1	0.03
Not available	3	0.06	10	0.27
Primary site				
Local bone only	15	0.30	8	0.22
Local bone and pulmonal or/and lymph node metastases	8	0.16	2	0.05
Multifocal	21	0.42	17	0.46
Local soft tissue only	1	0.02	0	0.00
Not available	5	0.10	10	0.27
Local treatment modality				
Surgery only	12	0.24	5	0.14
Irradiation only	11	0.22	8	0.22
Surgery + irradiation	19	0.38	15	0.41
None	3	0.06	0	0.00
Not available	5	0.10	9	0.24
Previous graft				
No previous graft	14	0.28	31	0.84
Allogeneic graft once	1	0.02	0	0.00
Autologous graft once	24	0.48	1	0.03
Autologous graft twice or more	7	0.14	2	0.05
Not available	4	0.08	3	0.08

Table 1. (Continued)

Parameter	Group A (RIC, $n = 50$)		Group B (HIC, $n = 37$)	
	Number	Fraction	Number	Fraction
Donor HLA match				
Matched related	27	0.54	32	0.86
Matched unrelated	3	0.06	1	0.03
Mismatched[b]	20	0.40	4	0.11
Graft source				
BM only	8	0.16	25	0.68
PB only	39	0.78	9	0.24
BM + PB	2	0.04	0	0.00
CB only	1	0.02	0	0.00
Not available	0	0.00	3	0.08
Pretransplant status				
CR	22	0.44	20	0.54
PR	17	0.34	12	0.32
PD	10	0.20	4	0.11
Not available	1	0.02	1	0.03

[a]Including multifocal relapse in some patients.
[b]One or more allele mismatch in HLA class 1 and/or HLA class 2.
RIC, reduced-intensity conditioning; HIC, high-intensity conditioning; allo-SCT, allogeneic stem cell transplantation; HLA, human leukocyte antigen; BM, bone marrow; PB, peripheral blood; CB, cord blood; CR, complete remission; PR, partial remission; PD, progressive disease.

Table 2. Results

Parameter	Group A (RIC, $n = 50$)		Group B (HIC, $n = 37$)	
	Number	Fraction	Number	Fraction
Engraftment				
Success	47	0.94	32	0.86
Failure	3	0.06	4	0.11
Not available	0	0.00	1	0.03
aGvHD				
None	24	0.48	20	0.54
Limited	15	0.30	8	0.22
Extensive	10	0.20	6	0.16
Not available	1	0.02	3	0.08
cGvHD				
None	17	0.34	14	0.38
Limited	4	0.08	3	0.08
Extensive	3	0.06	2	0.05
NA due to death or last FU ≤ day 100	22	0.44	15	0.41
Not available	4	0.08	3	0.08
Outcome				
DOC	4	0.08	16	0.43
DOD	33	0.66	17	0.46
Alive at last FU	13	0.26	4	0.11
Median OS (months after allo-SCT)				
Median	7.9		4.4	
Range	0–67		0–213	

RIC, reduced-intensity conditioning; HIC, high-intensity conditioning; aGvHD, acute graft versus host disease; cGvHD, chronic graft versus host disease, FU, follow-up; DOC, death of complications; DOD, death of disease; OS, overall survival; allo-SCT, allogeneic stem cell transplantation.
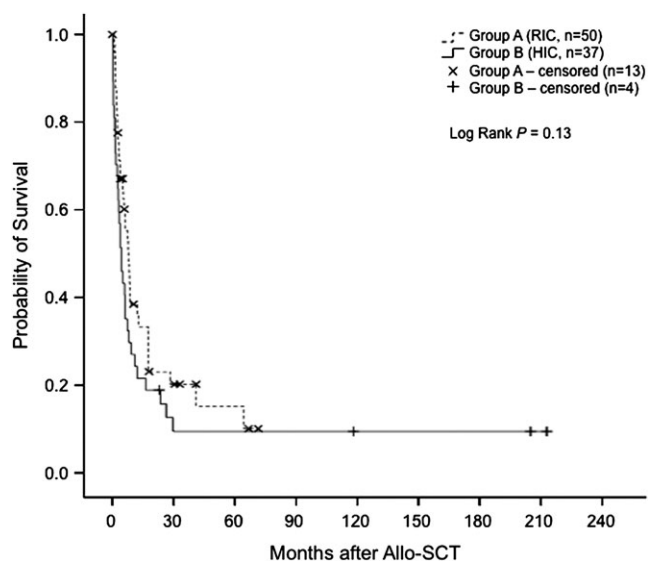
Figure 1. Overall survival probabilities from the date of allogeneic stem cell transplantation (allo-SCT) for patients treated with reduced-intensity conditioning (RIC; group A, $n = 50$) versus high-intensity conditioning (HIC; group B, $n = 37$) regimen; patients alive at last follow-up were censored. The differences are not significant (log rank, $P > 0.5$).

2.29–6.43) for group B patients, respectively. An overview is provided in Table 2.

relapse and DOD

The 5-year estimate for relapse/DOD was 0.81 (± 0.08) for group A patients and 0.47 (± 0.09) for group B patients. Overall, 33 of 50 (0.66) group A patients and 17of 37 (0.46) group B patients had a relapse and/or died of their disease (Table 2). Overall, risk of relapse/DOD was significantly higher within group A as compared with group B (Figure 2A, Gray's test $P = 0.009$).

death of complications

The 5-year and overall DOC estimate was 0.08 (± 0.04) for group A and 0.43 (± 0.08) for group B patients. Main reasons causing DOC were occurrences of infection, hemorrhage, veno-occlusive disease and GvHD. Overall, risk of DOC was significantly lower within group A as compared with group B (Figure 2B, Gray's test $P = 0.0002$).

HLA-mismatched versus HLA-matched grafts

In this setting, time periods from the date of the last allo-SCT until the occurrence of relapse/DOD were compared between those patients who had received HLA-mismatched with those who had received HLA-matched grafts. DOC was considered as a competing event for relapse/DOD. Twenty-four of 87 (0.28) patients had received HLA-mismatched and 63 of 87 (0.72) patients had received HLA-matched grafts. The 3-year estimate for relapse/DOD was 0.62 (± 0.13) for patients with HLA-mismatched grafts and 0.64 (± 0.06) for patients with HLA-matched grafts. The 3-year estimate for DOC was 0.22 (± 0.09) for patients with HLA-mismatched grafts and 0.24 (± 0.05) for patients with HLA-matched grafts. Neither group had an OS or
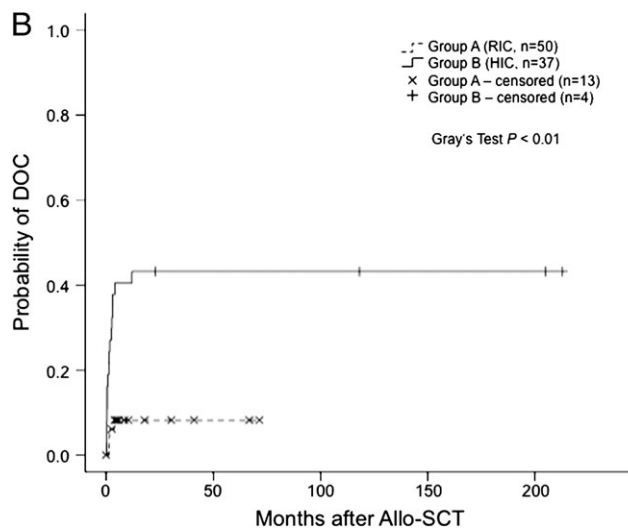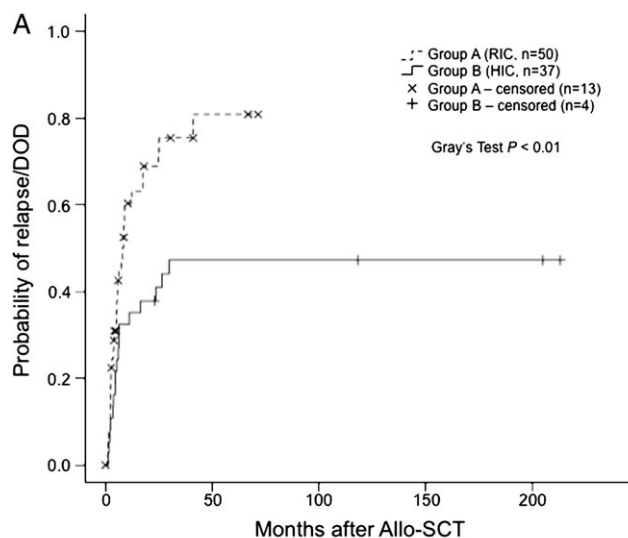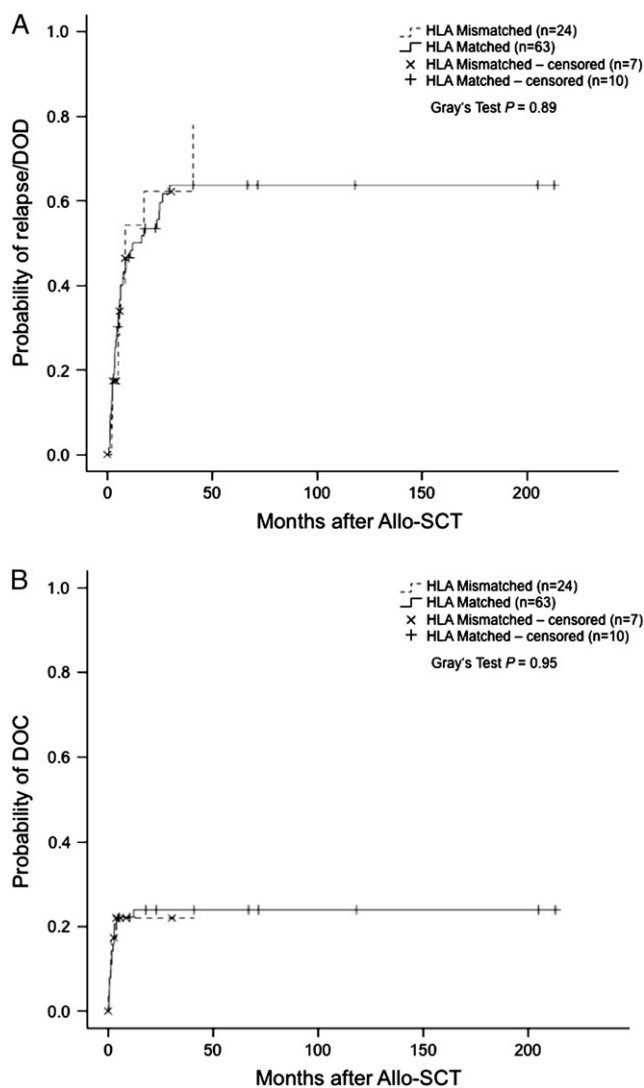

Figure 2. Probabilities and group comparisons of time periods from the date of allogeneic stem cell transplantation (allo-SCT) until (A) relapse/death of disease (DOD) and (B) death of complications (DOC) between patients treated with reduced-intensity conditioning (RIC; group A, $n = 50$) versus high-intensity conditioning (HIC; group B, $n = 37$) regimen in a competitive risk setting between DOD and DOC. Patients alive at last follow-up were censored. P values < 0.05 (Gray's test) indicate significant difference.

RFS advantage (Figure 3A, Gray's test $P = 0.89$; Figure 3B, Gray's test $P = 0.95$).

multivariate analysis

Upon multivariate analyses, none of the considered variables age, sex, conditioning regimen and disease stage at allo-SCT had an influence on OS outcome. Age just marginally failed to reach statistical significance as an influential factor for OS (Wald test $P = 0.05$). Employment of RIC was associated with an increased relapse/DOD versus DOC rate (Wald test $P = 0.021$) compared with HIC regimens (Table 3).

Figure 3. Comparison of survival rates in a competitive risk setting between relapse/death of disease (DOD) and death of complications (DOC) from the date of allogeneic stem cell transplantation (allo-SCT) until relapse/DOD (A) or until DOC (B) of patients receiving human leukocyte antigen (HLA)-mismatched or HLA-matched grafts. Patients alive at last follow-up were censored. Neither graft type provides a significant survival advantage (Gray's test, $P > 0.5$).

discussion

Allo-SCT has been applied as a therapeutic option for patients with AET [18]. Koscielniak et al. as well as Lucas et al. reported on AET patients who had experienced tumor regression following allo-SCT [20, 21]. However, the GvETE may be associated with toxicity of GvHD. In addition to natural killer cell-mediated toxicity, the broad T-cell allo-response poses a significant problem in clinical transplantation across HLA incompatibilities [24].

The use of myeloablative conditioning before allo-SCT has led to improved disease response but implicated pronounced treatment-related toxicity [14, 25–27], which in turn has led to a shift toward the implementation of less toxic RIC regimens in the last decade. This shift was expected to diminish incidence of

Table 3. Multivariate analysis

	HR	SE	95% CI	P value[a]
OS				
Recipient age	1.03	0.01	1.00–1.05	0.050
Sex				0.640
Male	Referent			
Female	0.88	0.27	0.52–1.50	
Conditioning				0.068
HIC	Referent			
RIC	0.60	0.28	0.35–1.04	
Disease stage at allo-SCT				0.110
RD	Referent			
CR	0.67	0.25	0.41–1.10	
Relapse/DOD				
Recipient age	0.99	0.02	0.95–1.03	0.500
Sex				0.580
Male	Referent			
Female	0.85	0.30	0.48–1.51	
Conditioning				0.021
HIC	Referent			
RIC	2.10	0.31	1.11–3.75	
Disease stage at allo-SCT				0.250
RD	Referent			
CR	0.71	0.30	0.40–1.27	

[a]Wald test.
HR, hazard ratio; SE, standard error; CI, confidence interval; OS, overall survival; RIC, reduced-intensity conditioning; HIC, high-intensity conditioning; RD, residual disease; CR, complete remission; allo-SCT, allogeneic stem cell transplantation; DOD, death of disease.

DOC and thus to enhance the conditions for a GvETE to engage. We retrospectively compared clinical outcome of allo-SCT in ET patients who had either received RIC (group A) or HIC (group B) before allo-SCT in regard to age at transplantation, toxicity, RFS and OS. Median age, disease stage and indications for allo-SCT were comparable. Both groups contained HLA-related and nonrelated matched and mismatched donor/recipient combinations, including haploidentical transplants. We hypothesized a clinically relevant GvETE in ET patients treated with allo-SCT and assessed its possible presence by comparing the relapse/DOD rates between both groups. In group A (RIC), DOC rate (0.08) was reduced and DOD rate (0.66) was increased compared with group B (HIC, DOC 0.43 and DOD 0.46). Compared with the application of HIC, RIC-mediated protection from DOC was significantly higher in uni- and multivariate analyses ($P < 0.05$). However, the lower DOC rate in the RIC-treated patients did not translate into improved survival but was associated with a higher relapse/DOD rate in group A as compared with group B and did not improve OS. Sex, disease status and age at allo-SCT were neither associated with improved time until relapse/DOD nor with OS in either setting.

Despite higher incidence of relapse/DOD due to lower incidence of DOC in patients treated with RIC, comparison of RFS and OS between both groups demonstrated that neither

type of conditioning was associated with significantly better survival rates. This finding indirectly implicates the lack of a clinically relevant GvETE in current settings. A DOC rate of 0.43 in patients receiving HIC confirms the results of our study conducted 10 years ago, which revealed a DOC rate of 0.40 in AET patients treated with matched allogeneic sibling grafts after HIC [18].

Some patients survived long term after allo-SCT and within this group some had received haploidentical grafts. We expected that the application of mismatched grafts would lead to protection via GvETE and therefore compared relapse/DOD and DOC outcomes of patients receiving HLA-matched versus HLA-mismatched grafts, but we could not detect any difference regarding RFS or OS. In anticipation of a supposed GvETE, the application of haploidentical transplantations in AET patients constitutes an approach that has been increasingly implemented notably during the last decade. In our study, among those patients who were alive at the time point of data censure, some had received haploidentical grafts just recently and were alive, so the long-term effect of this particular allo-SCT setting cannot yet be determined. Additionally, we did not address the role of donor lymphocyte infusions (DLI). Therefore, the question whether allo-SCT in haploidentical graft settings may yield a clinically relevant GvETE with or without the use of DLI will remain subject to ongoing prospective studies. As GvETE may depend on ET-specific as well as non-ET-specific antigen presentation, it will also be important to identify further biological eligibility criteria for haploidentical allo-SCT, i.e. certain HLA mismatch constellations when choosing the donor.

For data interpretation, it also has to be considered that group A (RIC) patients were mainly treated during the last 10 years in contrast to group B (HIC) patients who were mostly treated before this period. This might have an impact on DOC comparability between both groups, e.g. due to improvement in supportive therapy, especially for GvHD prophylaxis and treatment. Furthermore, initial and relapse systemic and local treatment differed between patients depending on center and time period and many group A patients had received prior grafts before allo-SCT. On the other hand, decreased relapse rates after HIC versus RIC provide further evidence for antitumor efficacy of high-dose therapy in ET.

Our results emphasize the need for additional therapeutic strategies for AET that yield antitumor effectiveness with minimal toxic side-effects. The identification of ET-specific target antigens [1] may give way to a personalized immune therapy using ET antigen-specific allo-restricted T cells in addition to the application of allo-SCT, rendering future application of DLI more specific and thus more efficacious and less toxic as seen in the treatment of other cancer entities [24, 28].

In our present study, we aimed to match patient groups as closely as possible, however, as the effect of allo-SCT demands large ET patient numbers, the effect of heterogeneity, i.e. regarding initial diagnostic and local/systemic therapeutic approaches [29–31] within our study population could not entirely be taken into account for assessment of comparability. This is why the conclusions drawn from the present data should be handled carefully. However, despite the limitations

associated with all retrospective studies, this is, to the best of our knowledge, the first study to provide a systematic assessment of outcomes of a large number of ET patients receiving allo-SCT in different therapeutic settings within Europe and beyond. A prospective international approach is warranted to further clarify the issue of allo-SCT in AET.

disclosure

The authors declare no conflict of interest.

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