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Allogeneic stem cell transplantation in patients with atypical chronic myeloid leukaemia: a retrospective study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation

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Summary

Atypical chronic myeloid leukaemia (aCML) is an aggressive malignancy for which allogeneic haematopoietic stem cell transplantation (allo-HSCT) represents the only curative option. We describe transplant outcomes in 42 patients reported to the European Society for Blood and Marrow Transplantation (EBMT) registry who underwent allo-HSCT for aCML between 1997 and 2006. Median age was 46 years. Median time from diagnosis to transplant was 7 months. Disease status was first chronic phase in 69%. Donors were human leucocyte antigen (HLA)-identical siblings in 64% and matched unrelated (MUD) in 36%. A reduced intensity conditioning was employed in 24% of patients. T-cell depletion was applied in 87% and 26% of transplants from MUD and HLA-identical siblings, respectively. According to the EBMT risk-score, 45% of patients were 'low-risk', 31% 'intermediate-risk' and 24% 'high-risk'. Following allo-HSCT, 87% of patients achieved complete remission. At 5 years, relapse-free survival was 36% and non-relapse mortality (NRM) was 24%, while relapse occurred in 40%. Patient age and the EBMT score had an impact on overall survival. Relapse-free survival was higher in MUD than in HLA-identical sibling HSCT, with no difference in NRM. In conclusion, this study confirmed that allo-HSCT represents a valid strategy to achieve cure in a reasonable proportion of patients with aCML, with young patients with low EBMT risk score being the best candidates.

Keywords: allogeneic transplantation, atypical chronic myeloid leukaemia, Myelodyslastic/Myeloproliferative Neoplasms (MDS/MPN), Ph-negative CML: *BCR-ABL1*-negative.

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Philadelphia-negative BCR-ABL1 negative chronic myeloid leukaemia (CML), usually called atypical CML (aCML), represents a very rare disease entity with aggressive clinical characteristics that usually confer a dismal prognosis (Kurzrock *et al*, 1990; Onida *et al*, 2002; Muramatsu *et al*, 2012; Wang *et al*, 2014). Even though high-throughput molecular studies have recently generated new insights into possible pathogenetic mechanisms (Maxson *et al*, 2013; Piazza *et al*, 2013; Li *et al*, 2014; Gambacorti-Passerini *et al*, 2015), which in the near future may translate into innovative targeted therapies (Gotlib *et al*, 2013), at present allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment option (Mittal *et al*, 2004). The disease is extremely rare, especially in patients younger than 65 years, and outcome after allo-HSCT has been reported only in small single-institution series (Koldehoff *et al*, 2004; Mittal *et al*, 2004; Lim *et al*, 2013). In this retrospective analysis, we describe allo-HSCT outcomes in patients with Philadelphia-negative, *BCR-ABL1*-negative CML reported to the European Society for Blood and Marrow Transplantation (EBMT) registry.

Patients and methods

This study, conducted on behalf of the Chronic Malignancies Working Party of the EBMT, was based on data from 42 patients with CML who underwent allogeneic stem cell transplantation from 1997 to 2006 and were reported as negative for the presence of the t(9;22)(q34;q11) cytogenetic translocation (Philadelphia chromosome) and for the *BCR-ABL1* transcript.

Main clinical and transplant characteristics were analysed for their association with different outcomes, i.e. overall survival (OS), relapse-free survival (RFS), relapse incidence (REL) and non-relapse mortality (NRM). All outcomes were calculated from the day of allo-HSCT. The Kaplan–Meier method was used for estimates of OS and RFS. REL and NRM were analysed by cumulative incidence estimates, considering these outcomes as each other's competing event. The log-rank test was used to compare survival curves and Cox-model based score tests were used to compare REL and NRM between groups (both tests being equivalent in models comparing a single factor).

The characteristics of interest are listed in Table I. Specifically, we included the covariates age (≤45 / >45 years), number of treatment lines preceding allo-HSCT (≤1 vs. >1), time interval elapsed between diagnosis and transplantation (<6 / 6–12 / >12 months), disease status at transplant (first chronic phase/more advanced phases), donor type [matched unrelated donor (MUD) *versus* human leucocyte antigen (HLA)-identical sibling], conditioning intensity [reduced intensity conditioning (RIC) *versus* standard myeloablative conditioning (MAC)], stem cell source [peripheral blood *versus* bone marrow (BM)], T-cell depletion (no/yes) and HSCT EBMT risk-score (0–2 / 3 / 4–7).

Calculations were performed with SPSS v.20 software (IBM Corp. Armonk, NY, USA). Cumulative incidences were calculated by means of SPSS macros developed by the Department of Medical Statistics and Bioinformatics of the Leiden University Medical Centre (Leiden, the Netherlands), on the basis of the hazard estimates from the Cox models. R version 3.3.0, with package 'prodlim' (R Foundation for Statistical Computing, Vienna, Austria), was used to create the figures. Institutional review board approval was obtained locally from all participating institutions.

Results

Table I lists the main patient, disease and transplant characteristics of the 42 patients included in the study. At the time of transplantation, 55% ($n = 23$) and 38% ($n = 16$) of patients were older than 45 and 50 years, respectively. At diagnosis, cytogenetics were missing in four patients (all reported as BCR/ABL1 negative).

A RIC regimen was employed in 24% of patients ($n = 10$), with a median age of 58 years (range 34–68),

Table I. Patient, disease and transplant characteristics.

Patients (*n*)	42
Sex (male/female)	23 (55)/19 (45)
Age (years)	Median 46, range 25–67
≤45 years	19 (45)
>45 years	23 (55)
Abnormal cytogenetics	9 (23)
Time from diagnosis to transplant (months)	Median 7, range 3–66
<6 months	11 (26)
6–12 months	18 (43)
>12 months	13 (31)
Splenectomy (pre-transplantation)	6 (19)
Pre- transplantation chemotherapy*	34 (94)
Disease stage at transplantation	
CP1	29 (69)
CP2	4 (10)
AP	5 (12)
BP	4 (10)
Donor type (HLA-identical sibling/MUD)	27 (64)/15 (36)
Conditioning (MAC/RIC)	32 (76)/10 (24)
SC Source (BM/PB)	14 (33)/28 (67)
T-cell depletion (yes/no)	22 (52)/20 (48)
EBMT Score	
Low (0–2)	19 (45)
Intermediate (3)	13 (31)
High (4–7)	10 (24)

Values in parenthesis are expressed in percentages.
AP, accelerated phase; BM, bone marrow; BP, blastic phase; CP1, first chronic phase; CP2, second chronic phase; EBMT, European Society for Blood and Marrow Transplantation; HLA, human leucocyte antigen; MAC, myeloablative conditioning; MUD, matched unrelated donor; PB, peripheral blood; RIC, reduced intensity conditioning.
*Out of 36 available.

Table II. Transplant, disease and survival outcome.

Transplant outcome*	
Graft failure	2
Acute GvHD grade II–IV	12
Limited chronic GvHD	12
Extensive chronic GvHD	9
Disease outcome†	
Complete response	26 (87%)
Partial response	2 (6·5%)
Non responder	2 (6·5%)
5-year outcome probability (95% confidence interval)	
Overall survival	51% (35–66%)
Relapse-free survival	36% (21–51%)
Relapse incidence	40% (25–55%)
Non-relapse mortality	24% (11–37%)

GvHD, graft-*versus*-host disease.
*Number of patients in which this outcome was reported.
†Out of 30 evaluable patients.

whereas MAC was preferred in all the others (median age 46 years, range 27–59). In the latter group, total body irradiation was included in the conditioning regimen in 56% of patients (n = 18). The stem cell source was the BM in 33% (n = 14) of patients, and was more often selected within the MAC than in the RIC transplant setting (41% vs. 10%, respectively). A T-cell depletion strategy was applied in 52% of cases (n = 22), and was more frequent in patients transplanted from a MUD than from an HLA-identical sibling (87% vs. 26%, respectively).

When the EBMT risk-score (Gratwohl *et al*, 1998) at transplant was calculated, 45% of patients were classified as 'low-risk' (score = 0–2), 31% were 'intermediate-risk' (score = 3) and 24% were 'high-risk' (4–7).

Primary graft failure was reported in two patients (5%), of whom one was transplanted from an HLA-identical sibling and one from a MUD. Following allo-HCST, 26 of the 30 evaluable patients achieved a complete remission of their disease, whereas a partial remission was reported in two patients. Two patients were classified as non-responders. Acute graft-*versus*-host disease (aGvHD) of grade II-IV occurred in 12 patients, whereas overall chronic GVHD

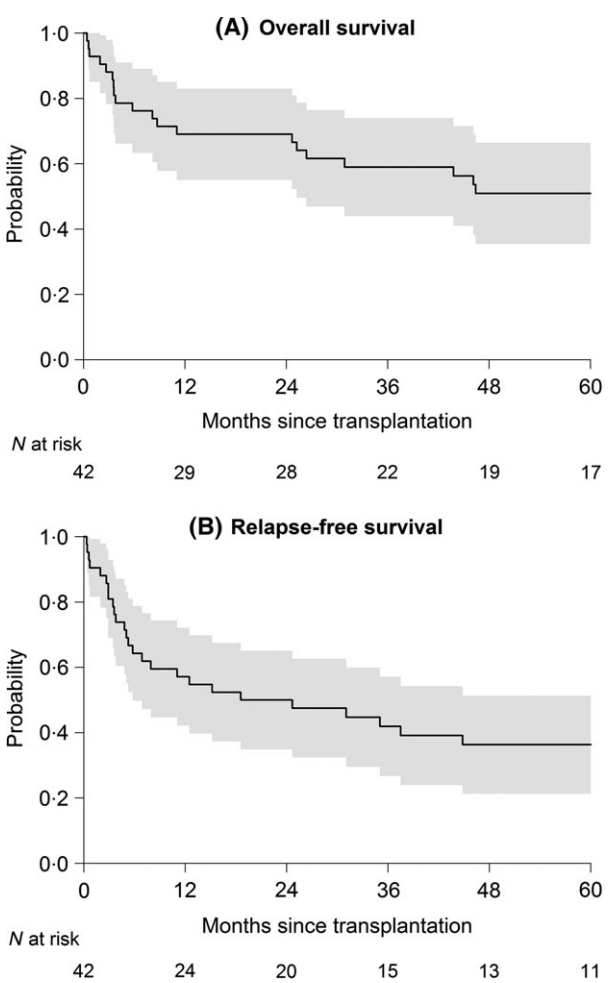

Fig 1. (A) Five-year overall survival following allogeneic transplantation in 42 patients. (B) Five-year relapse-free survival following allogeneic transplantation in 42 patients.

Table III. The impact of risk factors on OS and RFS at 5 years after allogeneic haematopoietic stem cell transplantation. Probabilities with 95% confidence intervals are provided. Hazard ratios with corresponding 95% confidence intervals are given. For each risk factor, the reference category is the first group. All *P*-values are from score tests based on Cox models testing overall differences. Significant risk factors are highlighted in bold.

	5-year OS			5-year RFS		
Risk factor	Probability (95% CI)	HR (95% CI)	*P*	Probability (95% CI)	HR (95% CI)	*P*
Overall	0·51 (0·35–0·66)			0·36 (0·21–0·51)		
Age			**0·036**			0·093
≤45 years	**0·66 (0·44–0·88)**			0·51 (0·27–0·74)		
>45 years	**0·39 (0·19–0·59)**	**2·54 (1·03–6·27)**		0·25 (0·07–0·43)	1·93 (0·89–4·19)	
Donor type			0·617			**0·042**
HLA	0·46 (0·26–0·65)			**0·22 (0·05–0·39)**		
MUD	0·60 (0·35–0·85)	0·8 (0·32–1·96)		**0·60 (0·35–0·85)**	**0·41 (0·17–0·99)**	
EBMT score			**0·034**			0·327
1–2	**0·65 (0·43–0·88)**			0·43 (0·19–0·67)		
3	**0·46 (0·19–0·73)**	**1·9 (0·67–5·44)**		0·31 (0·06–0·56)	1·45 (0·6–3·5)	
4–5–6	**0·30 (0·02–0·58)**	**3·62 (1·3–10·07)**		0·30 (0·02–0·58)	1·97 (0·79–4·92)	
Time from Dx to Tx			0·279			0·910
<6 months	0·55 (0·25–0·84)			0·36 (0·08–0·65)		
6–12 months	0·60 (0·37–0·83)	0·85 (0·29–2·54)		0·36 (0·12–0·59)	0·94 (0·38–2·35)	
>12 months	0·37 (0·10–0·64)	1·79 (0·64–5·06)		0·37 (0·10–0·64)	1·14 (0·44–2·97)	
Disease stage at Tx			0·086			0·071
CP1	0·57 (0·38–0·75)			0·43 (0·24–0·62)		
Other phase	0·38 (0·12–0·65)	2·08 (0·88–4·92)		0·32 (0·16–0·49)	1·99 (0·93–4·28)	
Stem cell source			0·783			0·723
BM	0·50 (0·24–0·76)			0·29 (0·05–0·52)		
PB	0·51 (0·32–0·70)	1·14 (0·46–2·79)		0·40 (0·21–0·59)	0·87 (0·4–1·89)	
Conditioning			0·248			0·584
MAC	0·45 (0·27–0·63)			0·32 (0·16–0·49)		
RIC	0·70 (0·42–0·98)	0·49 (0·15–1·67)		0·50 (0·19–0·81)	0·76 (0·29–2·02)	
T-cell depletion			0·249			0·884
No	0·60 (0·38–0·81)			0·34 (0·13–0·55)		
Yes	0·43 (0·21–0·64)	1·65 (0·7–3·88)		0·39 (0·18–0·60)	0·95 (0·45–1·99)	

95% CI, 95% confidence interval; BM, bone marrow; CP1, first chronic phase; DX, diagnosis; EBMT, European Society for Blood and Marrow Transplantation; HLA, human leucocyte antigen; HR, hazard ratio; MAC, myeloablative conditioning; MUD, matched unrelated donor; OS, overall survival; PB, peripheral blood; RFS, relapse-free survival; RIC, reduced intensity conditioning; Tx, transplantation.

(cGVHD) was reported in 21 of the patients alive at +100 days after transplantation ($n = 37$), being extensive in nine of them (Table II).

Median OS following allo-HSCT was 70 months [95% confidence interval (CI) 17–125] (Fig 1A). Median follow-up of patients alive was 89 months. The percentage of patients alive and relapse-free at 5 years after transplantation was 36% (Fig 1B) whereas NRM was 24%, and 40% experienced a disease-relapse following transplantation. Of the latter subgroup, 11 (26%) died from disease progression. Causes of non-relapse mortality included GvHD ($n = 1$), infectious complications ($n = 5$), organ damage/failure ($n = 2$) and other reasons ($n = 3$).

With regard to the association of the analysed risk factors with different outcomes (Tables III and IV), univariate analysis identified an age effect on OS, with patients older than 45 years having a significantly lower probability of survival at 5 years (39%, 95% CI 19–59%), compared to the younger subgroup (66%, 95% CI 44–88%; $P = 0·036$) (Fig 2). OS was also significantly affected by the EBMT risk score: patients in the high-risk group had a 5-year survival probability of 30% (95% CI 2–58%), compared to 46% (95% CI 19–73%) for patients in the intermediate risk group and 67% (95% CI 43–88%) for low-risk patients ($P = 0·011$) (Fig 3).

Donor type emerged as the only factor significantly associated with REL and RFS, favouring patients transplanted from an unrelated donor in comparison to those transplanted from an HLA-identical sibling. Relapses were significantly less frequent in patients transplanted with a MUD, with 13% (95% CI 0–31%) experiencing relapse over 5 years, compared to 55% (95% CI 35–75%; $P = 0·012$) in the HLA-identical transplant group (Fig 4A). As a consequence, patients transplanted with a MUD had a higher 5-year RFS probability (60%, 95% CI 35–85%), compared to patients transplanted from a HLA-identical donor (22%, 95% CI 5–39%; $P = 0·042$) (Fig 4B). No difference in NRM was observed between the HLA and MUD subgroups ($P = 0·89$).

Table IV. The impact of risk factors on REL and NRM at 5 years after allogeneic haematopoietic stem cell transplantation. Probabilities and 95% confidence intervals have been calculated as cumulative incidence functions in a competing risks setting. Cause specific hazard ratios with corresponding 95% confidence intervals are given. For each risk factor, the reference category is the first group. All *P*-values stem from score tests based on Cox models testing overall differences. Significant risk factors are highlighted in bold.

	5 year REL			5 year NRM		
Risk factor	Probability (95% CI)	HR (95% CI)	*P*	Probability (95% CI)	HR (95% CI)	*P*
Overall	0·40 (0·24–0·55)			0·24 (0·11–0·37)		
Age			0·361			0·122
≤45 years	0·39 (0·16–0·62)			0·11 (0·00–0·24)		
>45 years	0·40 (0·20–0·61)	1·57 (0·59–4·14)		0·35 (0·15–0·54)	2·74 (0·72–10·38)	
Donor type			**0·012**			0·889
HLA	**0·55 (0·35–0·75)**			0·23 (0·07–0·39)		
MUD	**0·13 (0·00–0·31)**	**0·22 (0·06–0·79)**		0·27 (0·04–0·49)	0·92 (0·26–3·18)	
EBMT score			0·875			0·215
1–2	0·46 (0·22–0·70)			0·11 (0·00–0·25)		
3	0·38 (0·12–0·65)	1·12 (0·37–3·42)		0·31 (0·06–0·56)	2·32 (0·52–10·37)	
4–5–6	0·30 (0·02–0·58)	1·37 (0·41–4·57)		0·40 (0·10–0·70)	3·56 (0·79–16·02)	
Time from Dx to Tx			0·991			0·864
<6 months	0·45 (0·16–0·75)			0·18 (0·00–0·41)		
6–12 months	0·42 (0·18–0·66)	0·95 (0·3–2·99)		0·22 (0·03–0·41)	0·93 (0·21–4·17)	
>12 months	0·32 (0·06–0·59)	1·02 (0·3–3·55)		0·31 (0·06–0·56)	1·34 (0·3–5·98)	
Disease stage at Tx			0·105			0·384
CP1	0·36 (0·18–0·54)			0·21 (0·06–0·36)		
Other phase	0·46 (0·19–0·73)	2·19 (0·83–5·77)		0·25 (0·10–0·40)	1·72 (0·5–5·94)	
Stem cell source			0·460			0·143
BM	0·29 (0·05–0·52)			0·43 (0·17–0·69)		
PB	0·46 (0·26–0·65)	1·52 (0·5–4·67)		0·14 (0·01–0·27)	0·42 (0·13–1·39)	
Conditioning			0·615			0·805
MAC	0·42 (0·25–0·60)			0·25 (0·10–0·40)		
RIC	0·30 (0·02–0·58)	0·73 (0·21–2·54)		0·20 (0·00–0·45)	0·83 (0·18–3·82)	
T-cell depletion			0·991			0·804
No	0·41 (0·19–0·63)			0·25 (0·06–0·44)		
Yes	0·38 (0·17–0·60)	1·01 (0·39–2·61)		0·23 (0·05–0·40)	0·86 (0·26–2·83)	

95% CI, 95% confidence interval; BM, bone marrow; CP1, first chronic phase; DX, diagnosis; EBMT, European Society for Blood and Marrow Transplantation; HLA, human leucocyte antigen; HR, hazard ratio; MAC, myeloablative conditioning; MUD, matched unrelated donor; NRM, non-relapse mortality; PB, peripheral blood; REL relapse incidence; RIC, reduced intensity conditioning; Tx, transplantation.

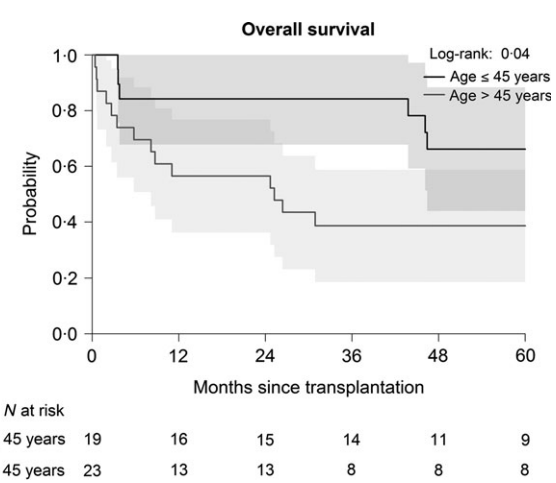

Fig 2. Five-year overall survival following allogeneic transplantation in 42 patients according to age (≤45 vs. >45 years).

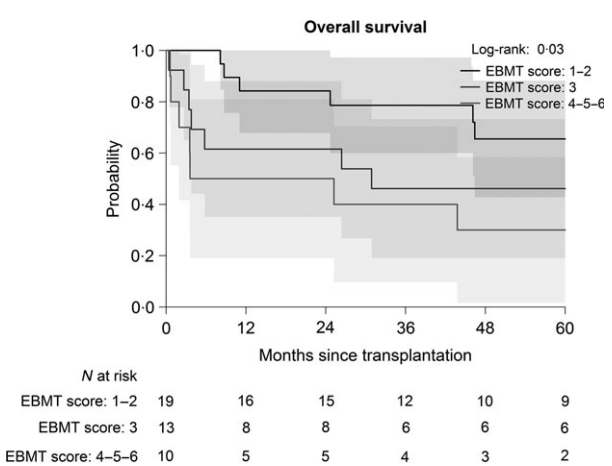

Fig 3. Five-year overall survival following allogeneic transplantation in 42 patients according to the European Society for Blood and Marrow Transplantation (EBMT) risk score.

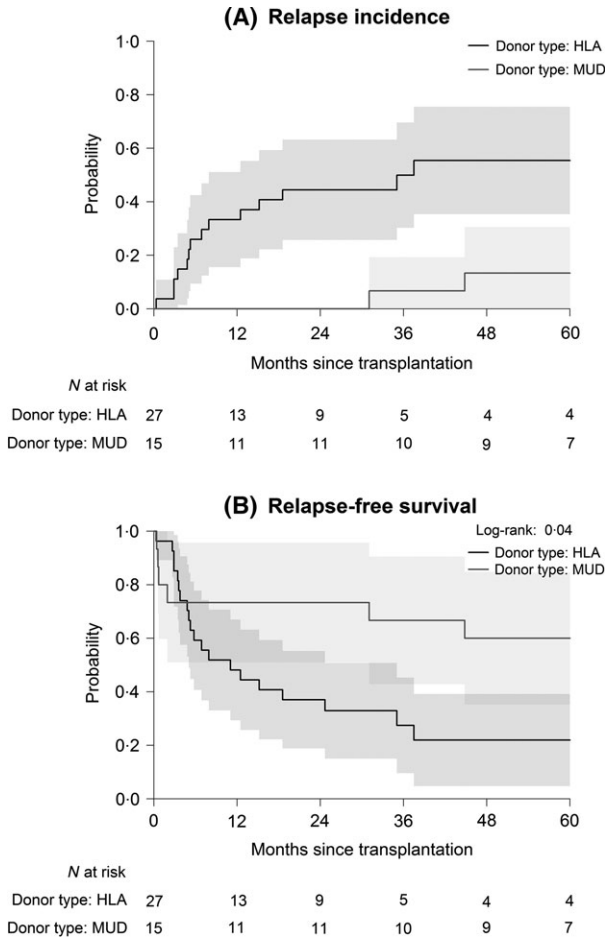

Fig 4. (A) Five-year relapse probability following allogeneic transplantation in 42 patients according to donor type (HLA-identical sibling *versus* matched unrelated). (B) Five-year relapse-free survival following allogeneic transplantation in 42 patients according to donor type (HLA-identical sibling *versus* matched unrelated). HLA, human leucocyte antigen; MUD, matched unrelated donor.

Discussion

Even if based on a limited population, this study includes the largest series of patients undergoing allo-HSCT for aCML assembled so far, both from related and unrelated donors. Study limitations come from its retrospective nature, encompassing cases transplanted with a heterogeneity of conditioning regimens (both standard and reduced intensity) in different stages of the disease (early or advanced), as well as having received a variety of pre-transplant treatment courses, possibly involving hydroxycarbamide, busulfan and α-interferon; splenectomy was also performed in a minority of patients. Nonetheless, considering that median OS of patients with aCML in the largest series ever reported is only 24 months (Onida *et al*, 2002), results arising from this analysis with a substantial number of patients being alive (51%, 95% CI 35–66%), and around one-third alive and disease-free 5 years after transplantation (36%, 95% CI 21–51%), appear to be of particular interest.

With regard to the prognostic factors capable of predicting post-transplant outcome, although their conclusive evaluation would necessarily require a prospective study in a larger patient population, our findings raise some interesting questions. Indeed, while longer survival was by no means unexpected in younger patients in comparison to their older counterparts, the significantly reduced risk of relapse associated with the use of unrelated *versus* HLA-identical sibling donor, also translating in a significantly longer RFS, is somehow surprising. Hence, in the absence of clear explanations for this finding, speculations on a possible more effective 'graft-*versus*-aCML', possibly related to minor antigens differences, rather than a possible impact of more efficacious conditioning regimens in the MUD setting, are entirely open to discussion.

Also of interest is the observed impact of the EBMT score on survival outcome. In fact, based on age of the patient, stage of the disease, time from diagnosis, donor type and donor-recipient gender combination, the EBMT score (Gratwohl score) has been originally created to assess the risk of death in patients with Philadelphia-positive CML undergoing allo-HSCT (Gratwohl *et al*, 1998). It provides a simple tool to predict outcome in terms of survival and NRM in patients who are candidates for transplantation. Since then, the EBMT score has also been effectively associated with transplant outcome in other acute and chronic haematological malignancies (Gratwohl *et al*, 2009). Its applicability in the setting of aCML has been previously suggested in a small series of patients from a single institution (Koldehoff *et al*, 2004). Indeed, when applied to our larger series of aCML patients, the EBMT score appeared able to discriminate three risk-groups with significantly different survival.

In conclusion, considering the current lack of effective treatment options for aCML, this study confirmed that allo-HSCT represents a valid strategy to achieve cure in a reasonable proportion of patients, with young patients that have a low EBMT risk score possibly being the best candidates.

Conflict of interest

The authors declare no conflict of interest.

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