Achievement of complete remission predicts outcome of allogeneic haematopoietic stem cell transplantation in patients with chronic myelomonocytic leukaemia. A study of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation

Achievement of complete remission predicts outcome of allogeneic haematopoietic stem cell transplantation in patients with chronic myelomonocytic leukaemia. A study of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation

Argiris Symeonidis[1], Anja van Biezen[2], Liesbeth de Wreede[2], Alfonso Piciocchi[3], Juergen Finke[4], Dietrich Beelen[5], Martin Bornhäuser[6], Jan Cornelissen[7], Liisa Volin[8], Ghulam Mufti[9], Yves Chalandon[10], Arnold Ganser[11], Benedetto Bruno[12,13], Dietger Niederwieser[14], Guido Kobbe[15], Rainer Schwerdtfeger[16], Theo de Witte[17], Marie Robin[18], Nicolaus Kröger[19,*] andfor the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation

[1]Haematology Division, Department of Internal Medicine, University of Patras Medical School, Patras, Greece.

[2]Department of Medical Statistics & Bioinformatics, Leiden University Medical Centre, Leiden, the Netherlands.

[3]GIMEMA Data Centre, Rome, Italy.

[4]Department of Medicine, Haematology, Oncology, University of Freiburg, Freiburg, Germany.

[5]Department of Bone Marrow Transplantation, University Hospital, Essen, Germany.

[6]Medizinische Klinik und Poliklinik I, Universitätsklinikum Technische Universität Dresden, Dresden, Germany.

[7]Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, the Netherlands.

[8]Stem Cell Transplantation Unit, Comprehensive Cancer Centre, Helsinki University Hospital, Helsinki, Finland.

[9]Department of Haematological Medicine, GKT School of Medicine, London, UK.

[10]Département des Spécialités de Médecine Service d'Hématologie, Hôpitaux Universitaires de Genève, and Faculty of Medicine, University of Geneva, Geneva, Switzerland.

[11]Department of Haematology, Haemostasis and Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany.

[12]Division of Haematology, Città della Salute e della Scienza di Torino, Torino, Italy.

[13]Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy.

[14]Division of Haematology, Oncology and Haemostasiology, University of Leipzig, Leipzig, Germany.

[15]Department for Haematology, Oncology and Clinical Immunology, University Hospital Dusseldorf, Heinrich Heine University, Dusseldorf, Germany.

[16]Deutsche Klinik fur Diagnostik, KMT Zentrum, Wiesbaden, Germany.

[17]Department of Tumourimmunology, Radboud University Medical Centre, Nijmegen, the Netherlands.

[18]Department of Haematology and BMT, Hopital Saint Louis, Paris, France.

[19]Department of Stem Cell Transplantation, University Medical Centre Hamburg, Hamburg, Germany.

ABSTRACT

Keywords: allogeneic stem cell transplantation;chronic myelomonocytic leukaemia;prognosis;WHO classification;survival

Summary

The results of allogeneic stem cell transplantation (allo-SCT) in chronic myelomonocytic leukaemia (CMML) are usually reported together with other categories of myelodysplastic syndrome. We analysed transplantation outcome in 513 patients with CMML, with a median age of 53 years reported to the European Group for Blood and Marrow Transplantation. Conditioning was standard (n = 249) or reduced-intensity (n = 226). Donors were human leucocyte antigen-related (n = 285) or unrelated (n = 228). Disease status at transplantation was complete remission (CR) in 122 patients, no CR in 344, and unknown in 47. Engraftment was successful in 95%. Grades 2–4 acute graft-versus-host disease (GvHD) occurred in 33% of the patients and chronic GvHD was reported in 24%. The 4-year cumulative incidence of non-relapse mortality was 41% and 32% for relapse, resulting in a 4-year estimated relapse-free and overall survival (OS) of 27% and 33%, respectively. Patients transplanted in CR had lower probability for non-relapse death (P = 0·002) and longer relapse-free and OS (P = 0·001 and P = 0·005, respectively). In multivariate analysis the only significant prognostic factor for survival was the presence of CR at transplantation (P = 0·005). Allo-SCT remains a curative treatment option for patients with CMML and should preferably be performed early after diagnosis or after establishing the best possible remission status.

Chronic myelomonocytic leukaemia (CMML) is a clonal haematopoietic stem cell disorder sharing hybrid features of both a myelodysplastic syndrome (MDS) and a myeloproliferative neoplasm (MPN). The World Health Organization (WHO) 2000 classification characterized CMML as a hybrid MDS/MPN disorder, subdivided into two main sub-forms (Bennett, 2000). CMML patients

are classified according to their baseline white blood cell (WBC) count, and those presenting with $\leq 13 \times 10^9$/l WBC, not rapidly increasing, are classified as dysplastic CMML (CMML-D), whereas patients presenting with WBC $> 13 \times 10^9$/l, steadily increasing thereafter, are classified as proliferative CMML (CMML-P) (Bennett, 2000). CMML-D exhibits less prominent leucocytosis, a more stable clinical course and rather longer median survival. CMML-P is associated with more prominent leucocytosis, more rapid clinical course and shorter survival. The prognosis of this disease varies widely, with an overall survival (OS) ranging from a few months to many years. Nevertheless, it has been questioned whether an arbitrarily defined cut-off value of 13×10^9/l WBC at baseline can distinguish clearly two disease subtypes. A retrospective analysis of 213 patients identified anaemia, circulating blast cells, absolute lymphocyte count $>2{\cdot}5 \times 10^9$/l, and bone marrow (BM) blasts >10% as predictors of shorter OS (Onida et al, 2002). These four factors were used to create a prognostic score that could stratify disease risk (Onida et al, 2002). TheWHO 2008 classification distinguishes CMML according to the percentage of BM blasts, as CMML-1 (blasts < 10%) and CMML-2 (blasts ≥ 10%), and removed the dysplastic/proliferative characteristics from the subclassification (Vardiman et al, 2002). In recent years several prognostic scoring systems have been developed, most of which include cytogentic and molecular abnormalities (Itzykson et al, 2013; Patnaik et al, 2013; Such et al, 2013; Wassie et al, 2014). Standard treatment approaches include supportive transfusions, use of erythropoietin for the correction of anaemia and hydroxycarbamide or other single agents for controlling excess leucocytosis. More recently, the use of hypomethylating agents has been associated with a response rate of about 25%, less than what is usually observed in patients with classic MDS (Aribi et al, 2007; Wijermans et al, 2008). Imatinib may induce temporary responses in rare cases associated with the t(5;12) translocation (Magnusson et al, 2002). Despite all these approaches, the median survival from diagnosis is 20–25 months (Onida et al, 2002; Beran et al, 2007). Allogeneic stem cell transplantation (allo-SCT) is the only curable treatment, but few studies have focused on the factors and conditions that would favour or discourage the application of allo-SCT in CMML. In most reports, results of allo-SCT in CMML were analysed together with the results of MDS or MPN and therefore were not particularly informative for CMML (Demuynck et al, 1996; Arnold et al, 1998; Deeg et al, 2000; Mittal et al, 2004; Warlick et al, 2009). In a previous report from the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (CLWP-EBMT) on 50 patients transplanted mainly from human leucocyte antigen (HLA)-matched related donors, the estimated 5-year OS was 21% and the disease-free survival (DFS), 18% (Kröger et al, 2002). Earlier transplantation, male donor, use of unmanipulated grafts and occurrence of acute graft-versus-host disease (GvHD), favoured better DFS (Kröger et al, 2002). Results from the Mayo Clinic implied the existence of a graft-versus-CMML effect, because the relapse of some patients was controlled with donor lymphocyte infusions (DLI) (Elliott et al, 2006). According to the Seattle experience, neither the MD Anderson prognostic score nor the WHO classification but only a higher comorbidity score adversely influenced the outcome (Depil et al, 2004; Kerbauy et al, 2005). Nevertheless, the number of patients in these studies was small. The WHO classifications may have an impact on survival in general, but it is not known whether they also influence the outcome of patients undergoing allo-SCT. In addition, general prognostic factors, such as disease status at SCT, intensity of the conditioning regimen, stem cell source, T-cell depletion and GvHD may also affect transplantation outcome in this disease.

The main objectives of this retrospective study were (i) to analyse non-relapse mortality (NRM), relapse incidence, relapse-free survival (RFS) and OS after allo-SCT in CMML cases registered in the EBMT database and (ii) to identify general prognostic factors.

Patients and methods

By the end of 2010, 513 patients with CMML were transplanted and registered in the EBMT database. Patients younger than 18 years at time of transplantation or patients diagnosed with juvenile myelomonocytic leukaemia (JMML) were excluded from this analysis.

Statistics

The following factors were investigated in univariate analysis: patient's age at transplantation, cytogenetics, WHO classification of CMML, interval from diagnosis to transplant, the inclusion of total body irradiation (TBI) in the conditioning, intensity of the conditioning, stem cell source, in vivo and/or ex vivo T-cell depletion of the graft, HLA-type of the donor (related or unrelated), year of transplantation, disease status at transplantation [complete remission (CR) versus no CR], donor-recipient gender match and the manifestation of acute or chronic GvHD. CR prior to transplantation was defined by a marrow blast count below 5% and a normalization of peripheral blood counts for at least 4 weeks.

Statistical analysis was performed by using IBM spss Statistics for Windows, Version 20.0 (Armonk, NY, USA) and R http://www.R-project.org) software. The time intervals for all outcomes (OS, RFS, relapse incidence and NRM) were measured from the day of allo-SCT onward. RFS indicates the probability of being alive and relapse-free. Differences between groups in OS and RFS were assessed by the log rank test. The impact of GvHD was investigated by means of Cox models, in which acute GvHD or chronic GvHD was entered as a time-dependent event. Relapse and NRM were considered as competing events and were analysed by means of cumulative incidence curves, comparing groups by a score test in a Cox model with a single factor (equivalent to the log rank test for OS and RFS). Cox proportional hazards regression models were fitted to examine the impact of risk factors on time to event outcomes. All significant variables identified by univariate analysis and clinical factors important for CMML were used to develop the multivariate model. Significant factors were identified by means of stepwise forward and backward selection. Confidence intervals were estimated at 95% level; all tests were two-sided, accepting $P < 0{\cdot}05$ as indicative of a statistically significant difference.

Results

A total of 513 patients with CMML transplanted before 31 December 2009 and registered in the EBMT database were analysed in this study. The male to female ratio was 2·01, and the median age at transplantation was 53·1 years. Two hundred and fourteen (41·7%) were transplanted when aged ≤50 years, whereas the remaining 299 patients (58·3%) were >50 years old at transplantation. Allo-SCT was performed at a median of 9 months following initial diagnosis of CMML. The karyotype was available in 164 patients; 60 patients had various cytogenetic abnormalities. Due to the limitation of availability of detailed cytogenetic data we could classify the patients only according to normal and ‘abnormal’ cytogenetics. One hundred and twenty-eight patients (28%) had not received any disease modifying treatment before allo-SCT, whereas 338 patients (72%) had been treated with an interventional approach and of those, 43% had primary refractory or relapsed/progressive disease and 26% were in complete remission at time of transplantation. Demographic and cytogenetic data of the analysed patient population, as well as data concerning WHO 2000 and WHO 2008 classification, the intensity of the conditioning regimen, administration of TBI in the conditioning, donor/recipient relationship and matching, disease status at transplantation, stem-cell source, T-cell depletion of the graft and the period of transplantation are

presented in Table 1.

Table 1. Patient demographics, disease- and procedure-features

Demographics	$n = 513$
Age at SCT; median (range), years	53·1 (18·5–75·4)
Male (n, %)	343 (66·9)
Female (n, %)	170 (33·1)
WHO Classification 2000, 2008	$n = 183$, $n = 214$
WHO 2000: CMML-D (n, %)	73 (39·9)
WHO 2000: CMML-P (n, %)	110 (60·1)
WHO 2008: CMML-1 (n, %)	87 (40·7)
WHO 2008: CMML-2 (n, %)	32 (15·0)
WHO 2008: secondary acute myeloid leukaemia (n, %)	95 (44·3)
Cytogenetic analysis	$n = 164$
Karyotype available (n, %)	164 (94·0)
Karyotype normal (n, %)	104 (63·4)
Karyotype abnormal (n, %)	60 (36·6)
Interval from diagnosis to SCT: median (range), months	9·0 (0·7–302·2)
Disease status at SCT	$n = 466$
CR (n, %)	122 (26·2)
Refractory/relapsed disease (n, %)	216 (46·4)
Untreated (n, %)	128 (27·4)
Conditioning	$n = 475$
Standard (n, %)	249 (52·4)
Reduced intensity (n, %)	226 (47·6)
Stem cell source	$n = 513$
BM (n, %)	119 (23·2)
PB (n, %)	394 (76·8)
T-cell depletion	$n = 491$
No (n, %)	295 (60·1)
Yes (n, %)	196 (39·9)
Ex-vivo (n, %)	20 (10·2)
In-vivo (n, %)	162 (82·7)
Both (n, %)	14 (7·1)
Donor	$n = 513$
Identical sibling (n, %)	276 (53·8)
Matched other related (n, %)	9 (1·8)
Matched unrelated (n, %)	106 (20·7)
Unrelated (n, %)	122 (23·8)
Year of SCT	$n = 513$
<1998 (n, %)	60 (11·7)
1998–2002 (n, %)	105 (20·5)
2003–2006 (n, %)	148 (28·8)
>2006 (n, %)	200 (39·0)

CMML-D, chronic myelomonocytic leukaemia dysplastic type; CMML-P, chronic myelomonocytic leukaemia proliferative type; CMML-1, chronic myelomonocytic leukaemia type 1 (<10% BM blasts); CMML-2, chronic myelomonocytic leukaemia type 2 (≥10% BM blasts); SCT, stem cell transplantation; CR, complete response; BM, bone marrow; PB, peripheral blood.

Engraftment and GvHD

Engraftment was successful in 95% of the patients, 19 patients (3·9%) did not engraft and the graft was lost in the remaining 4 patients (0·8%). Acute GvHD of grade 0–1 occurred in 315 patients

(67%), and grade 2–4 in 155 (33%). Maximum chronic GvHD was reported in 374 patients, it was absent in 106 (28%), limited in 58 (15%) and extensive in 65 patients (17%).

Non-relapse mortality

At the time of this analysis 277 patients have died (54%) of whom 103 (37%) died after relapse or disease progression. The cumulative incidence of NRM at one and at 4 years was 31% and 41%, respectively. One hundred and seventy-four patients died from NRM; causes of death were GvHD (23%), infectious complications (31%), toxicity and multi organ failure (19%) or other causes (27%). The NRM was significantly lower when the transplant was performed after 2002 (26% vs 40%, P = 0·006) (Fig 1) and lower (borderline significant) if the transplant was performed in the first year after diagnosis (29% vs 34%, P = 0·07). The NRM at 1 year did not differ significantly between CMML-1 (27%), CMML-2 (34%) and secondary/transformed acute myeloid leukaemia (sAML) (25%, P = 0·91).

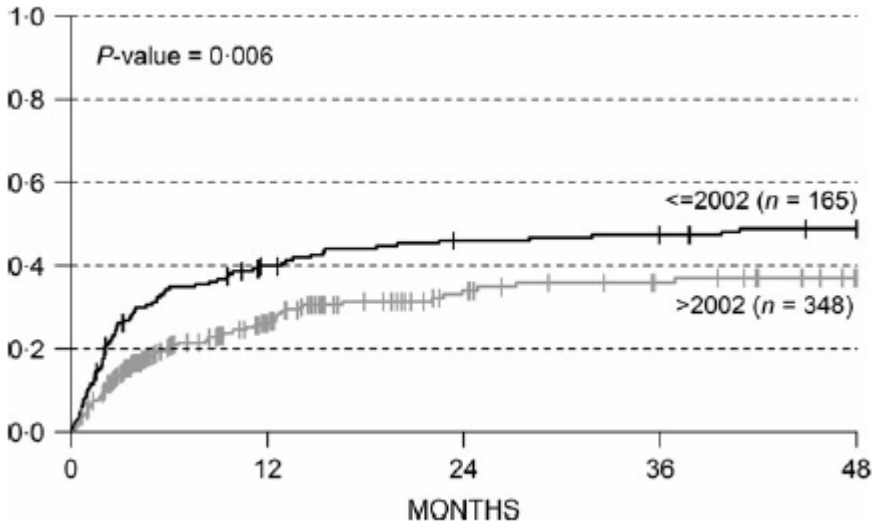

Figure 1. Cumulative incidence of non-relapse mortality according to time of transplantation (before 2002 and after 2002).

Relapse/relapse-free and OS

The cumulative incidence of relapse at 4 years was 32%, resulting in an estimated 4-year RFS and OS of 27% and 33%, respectively (Table 2).

Table 2. Results

	n (%)
Non-relapse mortality	
At 1 year	31
At 4 years	41
Cumulative incidence of relapse at 4 years	32
Relapse-free survival at 4 years	27
Overall survival at 4 years	33

Impact of WHO 2000 and WHO 2008 classification

Information regarding the WHO 2008 classification in CMML was available for 210 patients, 87 of whom were classified as CMML-1, 32 patients as CMML-2 and 95 patients as sAML evolving from previous CMML. There was no significant difference between CMML-1, CMML-2 and sAML regarding incidence of relapse at 4 years: 34% vs. 42% (P = 0·19), RFS at 4 years: 27% vs. 21% vs. 20% (P = 0·39) and OS at 4 years: 30% vs. 26% vs. 33% (P = 0·54). Additionally, according to the WHO 2000 classification, 73 out of 183 patients were classified as CMML-D (39·9%) and 110 as CMML-P (60·1%). There was no significant impact of the WHO 2000 classification on RFS, OS and any other transplantation outcomes. Similarly, the Kaplan–Meier (K-M) estimates for RFS and for OS were not significantly different in patients with CMML-1, CMML-2, sAML and CMML of unspecified type (data not shown).

Impact of disease status at transplantation

Relapse incidence was not different between patients transplanted in CR and those who were not in CR at transplantation. However, K-M estimates of both RFS and OS were significantly longer for patients transplanted in CR {median 20·8 months [95% confidence interval (CI) 7·5–34·2] vs. 7·6 months (95% CI 6·1–9·0), P = 0·001, and a median of 29·8 months (95% CI 4·0–55·6), vs. 12·4 months (95% CI 10·0–14·8) P = 0·005, respectively}. K-M probabilities for RFS and OS at 48 months were higher among patients transplanted in CR (36% vs. 24% and 42% vs. 30%, respectively) whereas the probability of non-relapse death at 1 year was lower (25% vs. 33%, P = 0·002). Thus, being in CR at transplantation, significantly affected outcome in allotransplanted patients with CMML in this analysis (Fig 2).

Table 3. Factors affecting transplantation outcome in univariate analysis. P-values are derived from score-tests in univariate Cox models (equivalent to log-rank test)

	NRM at 1 year (%)	*P*-value	Relapse at 4 years (%)	*P*-value	RFS at 4 years (%)	*P*-value	OS at 4 years (%)	*P*-value
Age ≤ 50 years/age > 50 years	32/30	0·93	30/34	0·30	28/25	0·45	34/32	0·79
CR/non CR at transplantation	25/33	**0·002**	32/33	0·11	36/24	**0·001**	42/30	**0·005**
CMML-1/CMML-2/sAML	27/34/25	0·91	34/42/46	0·19	27/21/20	0·39	30/26/33	0·54
Normal cytogenetics/abnormal cytogenetics	28/23	0·53	35/49	**0·07**	24/19	0·38	36/18	0·09
Interval between diagnosis and transplantation <12/≥12 months	29/34	**0·07**	32/34	0·19	29/22	**0·03**	34/30	**0·07**
MAC/RIC	33/26	0·53	32/37	0·37	27/24	0·89	34/31	0·91
Non-TBI/TBI	32/29	0·66	32/32	0·51	25/28	0·92	36/29	0·82
BM/PBSCT	38/28	0·14	31/32	0·66	24/28	0·16	31/34	0·28
Matched related donor/matched unrelated donor	29/33	0·14	35/30	0·29	27/26	0·66	34/31	0·14
CMML dysplastic/proliferative type	30/28	0·80	43/39	0·21	17/20	0·29	22/27	0·70
No T-cell depletion/T-cell depletion	30/31	0·70	32/35	0·67	30/20	0·99	35/27	0·49
Year of transplantation ≤2002/>2002	40/26	**0·006**	26/38	0·22	26/25	0·21	29/36	0·13

CR, complete remission; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; BM, bone marrow; PBSCT, peripheral blood stem cells; sAML, secondary acute myeloid leukaemia; NRM, non-relapse mortality; RFS, relapse-free survival; OS, overall survival. Significant and clinically relevant P-value are given in bold value.

Multivariate analysis

We performed a multivariate analysis to investigate the following factors, which might influence transplantation outcome including disease-related factors (WHO 2001 and WHO 2008 classification, disease status at transplantation), patient-related factors (age at transplantation, time interval between diagnosis and transplantation) and procedure-related factors (chronological period of transplantation, standard versus reduced intensity conditioning (RIC), stem-cell source, donor type, T-cell depletion). The only factor with a clear impact on survival was disease status at transplantation, and patients transplanted not in CR had significantly decreased RFS and OS compared to those transplanted in CR [Hazard ratio (HR) for RFS = 1·65, P = 0·001; HR for OS = 1·55, P = 0·005].

Discussion

Chronic myelomonocytic leukaemia (CMML) is difficult to treat and its course is rarely influenced by the available treatment approaches used in patients with MDS or MPN (Bacher et al, 2011). Therefore, allo-SCT appears a rational and attractive approach for patients with a suitable stem-cell donor. In a previous report from the CLWP-EBMT on 50 patients transplanted mainly from HLA-matched-related donors, the estimated 5-year OS was 21% and DFS was 18% (Kröger et al, 2002). Earlier transplantation, male donor, use of unmanipulated grafts and occurrence of acute GvHD favoured better DFS. There was a trend for a lower probability of relapse in patients exhibiting grade II-IV acute GvHD, and for a higher relapse rate in patients with T cell-depleted grafts, suggesting a 'graft-versus-CMML effect' (Kröger et al, 2002). Such an effect was also demonstrated from the analysis of the Mayo Clinic, according to which two of the five patients who relapsed post-allo-SCT and received DLI achieved durable remissions for more than 15 months

(Elliott et al, 2006). Some encouraging results have been obtained in Lille where DLI administration to 14 patients resulted in durable CR in 2 of them (Depil et al, 2004). Results from Seattle on 43 patients showed that 41% of them remained alive at 4 years post-transplant (Kerbauy et al, 2005). In this study neither the MD Anderson prognostic score nor the WHO classification had any influence on the outcome. The only factor that affected OS was a higher comorbidity score (Kerbauy et al, 2005). Similar results were obtained by other investigators analysing transplantation outcomes of patients with MDS and AML (Elliott et al, 2006; Boehm et al, 2008). The importance of early transplantation was also noted in an earlier study of 21 patients from Seattle (Zang et al, 2000). Promising, although not mature, are the results of the analysis of 20 patients from MD Anderson of whom 8 had CMML (Mittal et al, 2004). After a median follow-up time of 17·5 months, the actuarial OS at 2 years was 47%, and the DFS was 37% (Mittal et al, 2004). Nevertheless, in these retrospective studies the number of patients was usually small, some also included paediatric patients and in others results of CMML were not reported separately. Our study has analysed the largest cohort of transplanted adult patients with CMML ever published and has not included paediatric patients or patients with JMML. Our analysis has demonstrated that allo-SCT may be a curative approach for more than one quarter of the patients, as 29% of them were long-term survivors beyond 60 months, and 26% were relapse-free with almost no additional events occurring after 36 months post-transplant.

An interesting issue is the relevance of WHO classifications. Both systems have an impact on survival in non-transplanted patients, but it was not known whether they might influence transplantation outcome in patients undergoing allo-SCT. In our study there was a trend for improved RFS and OS for CMML-P vs. CMML-D as well as for CMML-1 vs. CMML-2 but, taking the relatively low number of patients with available data for WHO classification into account, we could not show that either WHO 2000 or WHO 2008 classification had any impact on the outcome, implying that the two classification systems do not describe different diseases but rather different phases of the same disease. Similar results were obtained from an analysis of 85 patients transplanted in American centres (Eissa et al, 2011). In this study, age, comorbidity index, pre-transplant haematocrit and karyotype had a statistically significant impact on the outcome. However, the analysis also included paediatric patients who might have contributed to the better long-term outcome (Eissa et al, 2011). The significance of karyotype has also emerged from the analysis of the results from the King's College Hospital in London (Krishnamurthy et al, 2010), whereas in our analysis the karyotype did not influence NRM, RFS and OS but showed borderline significance ($P = 0{\cdot}07$) for a higher risk of relapse for those patients with abnormal karyotype. However, due to the limitation of reported cytogenetic data in the registry it is very likely that more detailed information on cytogenetics, such as complex karyotype or monosomal karyotype, would show significant impact on outcome, as has been shown for MDS (Koenecke et al, 2015).

We were unable to identify any procedure-related parameters, such as the intensity of the conditioning regimen, the stem-cell source, T-cell depletion of the graft, the type of donor etc., with an impact on the transplantation outcome. This has also been confirmed by other studies (Kerbauy et al, 2005) and is especially interesting, because it indicates that allo-SCT should be performed whenever a suitable donor is available and that ‘technical’ details do not influence the outcome. In this regard RIC regimens are not inferior to standard regimens and, in particular, can be applied to older and frailer patients. The efficacy of a RIC regimen has been demonstrated in a previous prospective trial of 37 patients with MDS/sAML, including three patients with CMML (Kröger

et al, 2003) The use of RIC regimens may permit the application of allogeneic SCT in a broader patient population with acceptable toxicities (Laport et al, 2008).

Our final analysis failed to demonstrate any significant impact of the presence and grading of acute and chronic GvHD. Acute GvHD, analysed as a time-dependent covariate, was not a significant factor for survival. The role of chronic GvHD might be similar to that in other diseases. However, given that the significance of this parameter has not been proven in the present analysis, the usefulness of administering post-transplant DLI to manage relapses remains at least controversial and certainly deserves to be studied in a prospective randomized trial.

Thus, in our study, as also in others (Arnold et al, 1998; Laport et al, 2008; Warlick et al, 2009; Krishnamurthy et al, 2010) the most important parameter affecting transplantation outcome was disease status at the time of transplantation, and patients transplanted in CR clearly had a longer EFS and OS. Similar results have been obtained from retrospective analyses on patients with various other haematological dyscrasias, including MDS and AML. The clear message is that patients with CMML should be transplanted after achievement of the best possible remission status, either with combination chemotherapy or with epigenetic modifiers. In addition, early transplantation also appears to favourably influence the outcome of these patients.

Conflict of interest

There are no conflicts of interest to declare.

Author contributions

AS and NK designed the study, interpreted the data and wrote the manuscript. AvB collected the data from EBMT database. LvW and AP performed statistics. JF, DB, MB, JC, LV, GM, YC, AG, BB, DN, GK, RS, TdW and MR contributed patients and discussed the results. All authors approved the final manuscript.

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