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ORIGINAL ARTICLE

Outcomes of adults with active or progressive hematological malignancies at the time of allo-SCT: a survey from the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

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Previous data suggested that allo-SCT might be an effective therapy in the setting of chemo-refractory/relapsed diseases because of the potent long-term immune-mediated tumor control. This retrospective study aimed to analyze the outcome of adult patients who received allo-SCT in a chemo-refractory/relapsed status. The series included 840 patients with active or progressive disease at the time of transplant. Median age was 50 years. With a median follow-up of 40 months, 3-year OS, disease-free survival (DFS), and non-relapse mortality rates were 29 ± 2, 23 ± 2, and 30 ± 2%, respectively. At the last follow-up, 252 patients (30%) were still alive (of whom 201 were in CR (24%). In a Cox multivariate analysis, the use of a reduced-intensity conditioning (RIC) before allo-SCT and use of an HLA-identical sibling donor remained independently associated with a better OS (hazard ratio (HR) = 0.82; 95% confidence interval (CI), 0.69–0.98, $P = 0.03$; and HR = 0.79; 95% CI, 0.66–0.93, $P = 0.006$, respectively). Also, a diagnosis of myelodysplastic syndrome/myeloproliferative disorder, Hodgkin lymphoma and non-Hodgkin lymphoma compared with acute leukemia had a favorable impact on OS (HR = 0.55; 95% CI, 0.45–0.68, $P < 0.0001$; HR = 0.49; 95% CI, 0.31–0.75, $P = 0.001$; and HR = 0.47; 95% CI, 0.35–0.63, $P < 0.0001$, respectively). In conclusion, this study suggests that allo-SCT may be of benefit in some subgroups of patients with active or progressive hematological malignancies at the time of allo-SCT.

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INTRODUCTION

Allo-SCT represents a potentially curative treatment in a large variety of hematological malignancies. After allo-SCT, patients may benefit from a potent immune-mediated graft-versus-tumor effect (GVT).[1] Such a GVT effect can induce long-term remission by itself.[2] Also, the benefit of the GVT effect may be further increased by the anti-tumor effect of the conditioning regimen administered before the graft. Thus, both activities contribute to achieving cure in patients.[3,4] In recent years, eligibility criteria for allo-SCT have been expanded progressively with the use of unrelated donors and cord blood as stem cell sources, as well as the use of reduced-intensity conditioning (RIC) regimens.[5,6] Also, disease status and genetic determinants have been consistently identified as major prognostic factors predicting outcomes in patients after allo-SCT.[3,4] Thus, those patients with active refractory/relapsed hematological diseases at transplant have less chance of achieving CR and long-term survival. Best supportive care and/or investigational drugs in phase 1 trials are usually proposed to these patients.[7,8] However, scarce data suggested that allo-SCT might be of potential benefit even in patients with chemo-refractory/relapsed disease, mainly because of the long-term immune-mediated disease control.[9,10] Currently, there are no large prospective trials assessing the outcome of patients with active refractory/relapsed hematological diseases at the time of allo-SCT according to the type of disease. The aim of this study was to analyze a series of 840 patients who received allo-SCT while in active refractory/relapsed disease at the time of transplant.

PATIENTS AND METHODS

Study design

This was a retrospective multicenter study assessing the results of allo-SCT in 840 patients with active refractory/relapsed hematological disease at the time of transplant and reported to the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) registry between January 2005 and December 2009. No selection criteria other than allo-SCT for patients

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with active or progressive disease (primary induction failure (PIF), active relapse, progression or blast crisis for CML) at transplant were used for the purpose of this study. The study was approved by the scientific council of the SFGM-TC and performed according to the SFGM-TC guidelines and in accordance with the principles of the declaration of Helsinki. Three hundred and thirty-seven (40%) females and 503 (60%) males were identified during the study period. The median age was 50 (range, 16–71) years.

Patients and transplant procedures

Patients', disease and transplant characteristics are summarized in Table 1. Between 2005 and 2009, 840 patients with various hematological diseases (AML, $n=309$; ALL, $n=45$; myelodysplastic syndrome (MDS), $n=150$, myeloproliferative disorder (MPD), $n=101$; CML, $n=26$; non-Hodgkin lymphoma (NHL), $n=98$; Hodgkin lymphoma (HL), $n=40$; multiple myeloma (MM), $n=38$; CLL, $n=24$; and biphenotypic leukemia, $n=9$) were treated with allo-SCT and reported to the SFGM-TC registry. In the NHL group, there were 36 patients with low-grade lymphoma, 15 with mantle cell lymphoma, 21 with a diffuse large B-cell/Burkitt lymphoma, 16 with a T-cell lymphoma and 10 with a non-classified lymphoma.

Relapse was defined as reoccurrence of disease while being in a CR status, whatever the disease. Progression was defined as progression of the disease while being in a persistent but stable and non-treated disease status, whatever the disease. Finally, PIF was defined as failure of one or two induction chemotherapy regimens while being in a newly diagnosed disease status, whatever the disease. Definitions did not include cytogenetics or molecular marker evaluations for leukemias while computed tomographic and positron-emission tomographic scans were both used in lymphomas to define status.

In this series, 224 patients presented with a PIF (acute leukemia (AL) $n=112$; MDS $n=64$; MPD $n=40$; NHL $n=5$; HD $n=2$, MM $n=1$), 353 were classified in active relapse (AL $n=251$; NHL $n=61$; HD $n=24$; CLL $n=4$; MM $n=13$), while 237 were classified in disease progression (MDS $n=86$; MPD $n=61$; CLL $n=20$; MM $n=24$; NHL $n=32$; HD $n=14$) and 26 (CML only) in blast crisis at the time of transplant. The median interval between diagnosis and transplant was 17 (range, 2–356) months. Twenty-nine percent of the patients ($n=242$) failed at least one previous SCT (autologous or allogeneic). Three hundred and fifty (42%) patients received allo-SCT from an HLA-matched sibling donor, while the remaining 58% received an allogeneic graft from a matched unrelated or mismatched donor. The stem cell source was mainly PBSCs ($n=598$; 71%). BM was used in 135 patients (16%) and cord blood in 102 patients (12%). Myeloablative conditioning regimen was used in 322 patients (38%), and various RIC regimens were used in other cases (62%).

Statistical analysis

Clinical outcomes that were collected and updated until March 2013 included demographic, disease and transplant characteristics, GVHD status, time to progression or relapse and survival. Standard criteria were used for GVHD assessment. Characteristics considered were recipient age ($\leqslant$ or $>$ median), type of disease (AL (AML + ALL), chronic leukemia (CLL + CML), MDS + MPD, lymphoma (HD, NHL), type of NHL, MM), status at transplant for AML (PIF vs relapse) and allo-SCT characteristics (type of donor: sibling vs other), type of conditioning regimen (standard myeloablative conditioning vs RIC) and stem cell source (cord blood vs others)). The primary endpoints were OS and PFS. Secondary end points were incidence of non-relapse mortality (NRM) and incidence of chronic GVHD. PFS was defined as survival without relapse or progression. NRM was defined as death without relapse/progression. Probability of OS and PFS were calculated using the Kaplan–Meier estimate while the log-rank test was used for univariate comparisons. Cumulative incidence curves were used for estimating NRM in a competing risk setting, considering death as competing event, and Gray test[11] was used for univariate comparisons. Death was also considered as a competing event for chronic GVHD. Association of patient and graft characteristics with outcomes were evaluated in multivariate analyses, using Cox proportional hazards for PFS and OS, and proportional sub-distribution hazard regression model of Fine and Gray[12] for NRM. The type I error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS Inc. (Chicago, IL, USA) and R 2.13.2 software packages (R Development Core Team, Vienna, Austria).

Table 1. Patients, disease and transplant characteristics

Characteristics	N *(%)*
Gender, male/female	503 (60)/337 (40)
Median age (years, range)	50 (16–71)
Diseases	
MDS	150 (18)
AML	309 (37)
ALL	45 (5)
Biphenotypic leukemia	9 (1)
CML	26 (3)
CLL	24 (3)
MPD	101 (12)
Hodgkin disease	40 (5)
Non-Hodgkin lymphoma	98 (11.5)
Multiple myeloma	38 (4.5)
Status at transplant	
Primary induction failure	224 (27)
Relapse	353 (42)
Progression	237 (28)
Blast crisis (CML)	26 (3)
Previous transplant	
None	588 (70)
One	206 (24.5)
Two or more	46 (5.5)
Previous autograft	163 (19)
Previous allograft	79 (9)
Median year of transplant (range)	2007 (2005–2009)
Median interval from diagnosis to transplant (range)	17 months (2–356)
Median follow-up (months, range)	40 (1–96)
Donor type	
HLA-matched related	350 (42)
HLA-mismatched related	10 (1)
HLA-matched unrelated	141 (17)
HLA-mismatched unrelated	107 (13)
Unknown unrelated	230 (27)
Unknown	2
Stem cell source	
PBSC	598 (71)
BM	135 (16)
Cord blood	102 (12)
PBSC + BM	4 (1)
Type of conditioning regimen	
Standard myeloablative	322 (38)
Reduced intensity conditioning	512 (62)
Unknown	6

Abbreviations: MDS = myelodysplastic syndrome; MPD = myeloproliferative disease.

RESULTS

Total study population

With a median follow-up of 40 (range, 1–96) months after allo-SCT for surviving patients, engraftment was observed in 90.4% of cases. Grade II–IV and grade III–IV acute GVHD occurred in 39.3% ($n=296/754$) and 19.2% ($n=145/754$) of patients, respectively. Chronic GVHD was observed in 239 patients (36%; limited form, $n=105$; extensive form, $n=107$; missing data, $n=27$). At last follow-up, 252 patients (30%) were still alive (of whom 201 were in CR; 24%). The Kaplan–Meier estimates of 3-year OS and PFS (Figure 1) were $29\pm2\%$ and $23\pm2\%$, respectively. The cumulative incidences of NRM and chronic GVHD were $30\pm2\%$ and $31\pm2\%$, respectively. In univariate analysis, factors associated with a higher

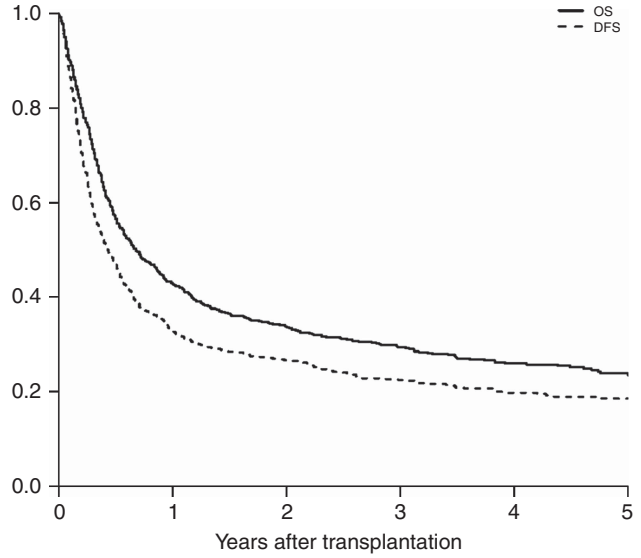

Figure 1. OS and PFS for the all cohort ($N = 840$).

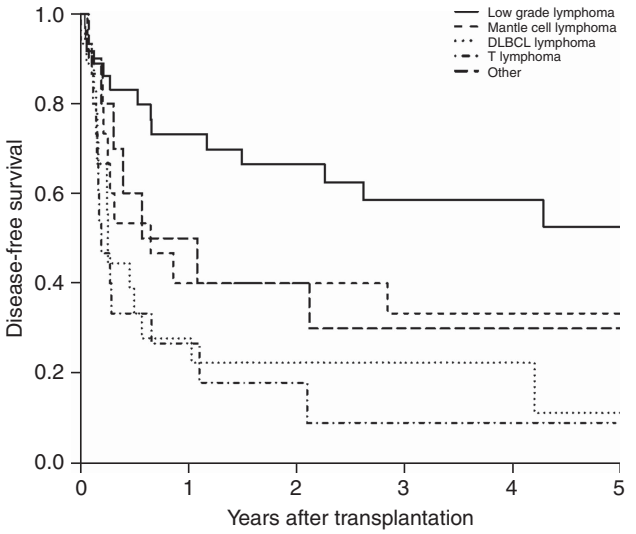

Figure 2. Comparison of PFS according to non-Hodgkin lymphoma subtype.

OS were the use of an HLA identical sibling donor (32 ± 3% vs 27 ± 2%, $P = 0.007$) and the use of a RIC regimen (34 ± 2% vs 23 ± 2%, $P = 0.003$). Also, the use of a RIC regimen was associated with a higher PFS (25 ± 2% vs 19 ± 2%, $P = 0.02$) while the use of a sibling donor was associated with a significantly lower NRM (25 ± 3% vs 33 ± 2%, $P = 0.004$). In a Cox multivariate analysis, the use of a RIC regimen and of a sibling donor remained independent factors associated with a better OS (HR = 0.82; 95% CI, 0.69–0.98, $P = 0.03$; and HR = 0.79; 95% CI: 0.66–0.93, $P = 0.006$; respectively). The use of a sibling donor was also associated with a lower NRM (HR = 0.68; 95% CI, 0.52–0.89, $P = 0.005$). The only difference between related and unrelated donor groups was a higher number of patients in the latter group allografted for the third time (7.5% vs 2.6%, $P = 0.002$). This may explain a lower NRM in the sibling group. Considering disease subtypes, a diagnosis of MDS/MPD, HL and NHL were associated with better OS (HR = 0.55; 95% CI, 0.45–0.68, $P < 0.0001$; HR = 0.49; 95% CI, 0.31–0.75, $P = 0.001$; and HR = 0.47; 95% CI, 0.35–0.63, $P < 0.0001$, respectively), compared with AL. A diagnosis of MDS/MPD and NHL were associated with better PFS (HR = 0.57; 95% CI, 0.47–0.7, $P < 0.0001$ and HR = 0.51; 95% CI: 0.38–0.67, $P < 0.0001$, respectively). None of the diseases was associated with lower NRM.

Finally, occurrence of chronic GVHD was associated in multivariate analyses with better OS (HR: 0.78; 95% CI: 0.61–0.99, $P = 0.04$) and lower RI (HR: 0.58; 95% CI: 041–0.82, $P = 0.001$).

ALs

OS and PFS for AL were relatively poor with a 3-year OS of 17 ± 2% and a 3-year DFS of 14 ± 2%. No significant difference between AML and ALL patients was observed in terms of 3-year PFS: 14 ± 2 for the former vs 12 ± 5% for the latter, $P = 0.97$. When considering only AML patients, a trend for higher PFS was observed in patients allografted after PIF compared with patients allografted in relapse: PIF: 18 ± 4%, first relapse: 14 ± 3%, second relapse: 8 ± 3%, $P = 0.06$.

Chronic leukemias in advanced phase

OS and PFS for chronic leukemias showed intermediate results with 2-year OS of 31 ± 7% and a 3-year PFS of 20 ± 6%. There was no significant difference between CLL and CML in terms of PFS (25 ± 10 and 16 ± 8, respectively; $P = 0.17$).

MDS/MPD

OS and PFS for MDS/MPD also showed intermediate results with a 3-year OS of 38 ± 3% and a 3-year PFS of 31 ± 3%. Three-year PFS was significantly higher for MPD patients compared with MDS patients (39 ± 5% vs 26 ± 4%, $P = 0.008$).

Lymphomas

For HL patients, 3-year OS and PFS were 49 ± 8% and 17 ± 6%, respectively. For NHL patients, 3-year OS and PFS were 47 ± 5% and 37 ± 5%, respectively. No significant difference was observed between NHL and HL in terms of DFS ($P = 0.07$). When considering NHL patients, 3-year PFS was significantly higher in patients with low-grade lymphoma: 58 ± 9% vs 33 ± 12% for mantle cell lymphoma vs 22 ± 10% for diffuse large B-cell lymphoma vs 9 ± 8% for T cell lymphoma vs 30 ± 15% for the non-classified lymphoma cases ($P = 0.001$; Figure 2).

MM

3-year OS and PFS for MM were 25 ± 8% and 14 ± 6%, respectively.

Figures 3 and 4 show the OS and PFS according to each disease subgroup.

DISCUSSION

The current study reports the largest series of adult patients receiving allo-SCT for active or progressive hematological malignancies at the time of transplant. Despite its retrospective nature and the inherent selection biases, our data support the use of allo-SCT in some subgroups, especially patients with lymphoid disorders. Focussing on a more recent period (2005–2009), a majority of patients in our series received a RIC allo-SCT, which was associated with a better outcome. As a consequence, this type of conditioning regimen should probably be preferred in this setting, as it can provide lesser toxicity compared with myeloablative regimens. The use of a sibling donor was also significantly associated with a better outcome in our series, as it was shown to be correlated with lower NRM compared with other sources of donors.

From a disease standpoint, results were quite disappointing in patients with active AML or ALL, CML in blast crisis or progressive MM at transplant, as 3-year PFS were 14, 12, 16 and 14%, respectively. The latter can be explained by the well-known poor GVT effect for high-risk AL, including blast crisis of CML and

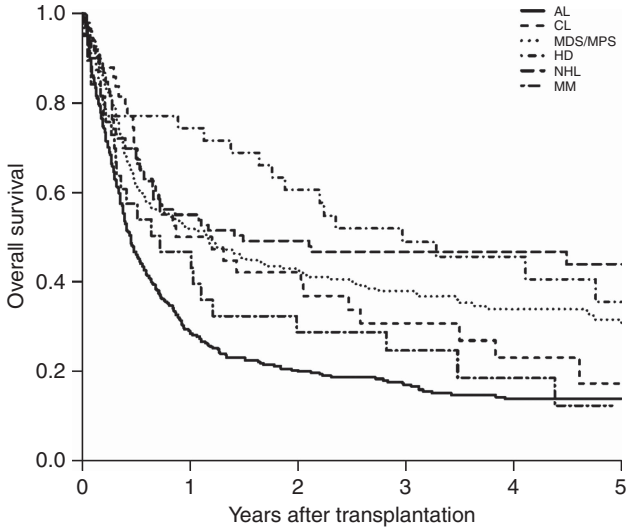

Figure 3. OS according to disease subtype.

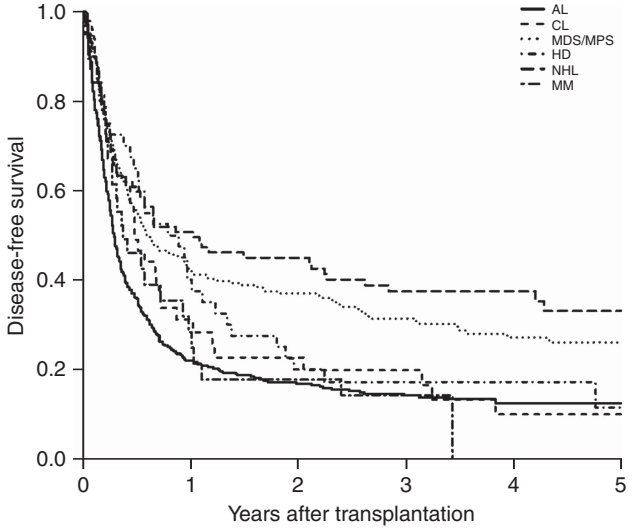

Figure 4. PFS according to disease subtype.

myeloma.[2] Such results are not completely surprising[10,13–19] reflecting also the dismal response of very fast-growing hematological diseases as well as the higher toxicity of the procedure in heavily pre-treated patients. However, these data may be tempered as better outcomes may be obtained in some selected subgroups according to pre-transplant variables, as previously described by Duval *et al.*[10] in patients with active relapsed/refractory AL after myeloablative conditioning regimens. Duval *et al.*[10] reported 3-year OS and NRM of 19% and 39%, respectively, for AML patients ($n = 1673$) and 16% and 41%, respectively, for ALL cases ($n = 582$). A prognostic scoring system could be established integrating five poor parameters for AML (first CR duration < 6 months, circulating blasts, non-HLA identical sibling donor, performance status $\leqslant 90\%$ and poor-risk cytogenetics). Four other good parameters were also identified for ALL (PIF or first untreated relapse, $< 25\%$ marrow infiltrating blasts, cytomegalovirus seronegative donor and age < 10 years), leading to a 3-year OS between 42% and 46% for patients with a score $= 0$ and between 22% and 28% for patients with a score $= 1$. Unfortunately, these variables could not be studied here.

For other diseases, including NHL, HL, CLL, MDS and MPD or AML in PIF, 3-year PFS was almost or superior to 20%, which compares favorably with results usually achieved with palliative strategies. The most interesting results were those obtained in NHL and HL, especially low-grade and mantle cell lymphomas, confirming previous published data mainly after RIC conditioning regimens.[20–24]

From a general point of view, in patient candidates for allo-SCT with active or progressive disease at the time of transplant, several challenges must be handled simultaneously. On the one hand, one must achieve disease control, and on the other hand one must reduce the toxicity of the procedure. Novel transplant approaches, namely, the so-called 'sequential approach' combining both the cytoreductive chemotherapy phase and the RIC regimen, have shown some promising results in refractory/relapsed AML.[9,25] Moreover, the increasing use of reduced toxicity myeloablative regimen (RTC regimen) based on fludarabine and myeloablative alkylating-agent doses (for example, i.v. BU or treosulfan) might represent an appealing backbone conditioning before allo-SCT, with sufficient safety, allowing exploration of additional therapies (for example, MoAbs, radio-immunotherapy) for further enhancing the antileukemic effect and preventing relapse.[26] Furthermore, it is likely that maintenance therapies should be considered in most of these patients in order to achieve long-term disease control after transplant.[27]

In conclusion, this analysis suggests that allo-SCT may be of some benefit as salvage therapy in specific subgroups of adult patients with active or progressive disease at the time of transplant. Increasing disease control with novel agents as a bridge to transplant,[28,29] and the use of maintenance strategies after allo-SCT, may allow for further optimizing the results of these highly poor-risk patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

PC conceived and designed the study, analyzed data, recruited patients, provided clinical care, performed bibliographic search and wrote the manuscript. MM conceived and designed the study, recruited patients, provided clinical care, analyzed data, performed bibliographic search and helped writing the manuscript. ML performed statistical analyses. NM, KB, GS, IY-A, MM, CEB, SM, YB, J-OB, DB, NM, GG, ED recruited patients, provided clinical care and commented on the manuscript. NR performed central data management and collection. All the authors approved the manuscript for publication purposes.

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