



Low non-relapse mortality and long-term preserved quality of life in older patients undergoing matched related donor allogeneic stem cell transplantation: a prospective multicenter phase II trial

Didier Blaise, Raynier Devillier, Anne-Gaelle Lecoroller-Sorriano, Jean-Marie Boher, Agnès Boyer-Chammard, Reza Tabrizi, Patrice Chevallier, Nathalie Fegueux, Anne Sirvent, Mauricette Michallet, et al.

► To cite this version:

Didier Blaise, Raynier Devillier, Anne-Gaelle Lecoroller-Sorriano, Jean-Marie Boher, Agnès Boyer-Chammard, et al.. Low non-relapse mortality and long-term preserved quality of life in older patients undergoing matched related donor allogeneic stem cell transplantation: a prospective multicenter phase II trial. *Haematologica*, 2015, 100 (2), pp.269-274. 10.3324/haematol.2014.113571 . hal-02167058

HAL Id: hal-02167058

<https://hal.science/hal-02167058>

Submitted on 27 Jun 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Low non-relapse mortality and long-term preserved quality of life in older patients undergoing matched related donor allogeneic stem cell transplantation: a prospective multicenter phase II trial

Didier Blaise,^{1,2,3} Raynier Devillier,^{1,2,3} Anne-Gaëlle Lecoroller-Sorriano,⁴ Jean-Marie Boher,⁵ Agnès Boyer-Chammard,⁵ Reza Tabrizi,⁶ Patrice Chevallier,⁷ Nathalie Fegueux,⁸ Anne Sirvent,⁸ Mauricette Michallet,⁹ Jacques-Olivier Bay,¹⁰ Sabine Fürst,¹ Jean El-Cheikh,¹ Laure Vincent,⁸ Thierry Guillaume,⁷ Caroline Regny,¹¹ Noël Milpied,⁶ Luca Castagna,¹ and Mohamad Mohty^{7,12,13}

¹Hematology Department, Transplantation Unit, Paoli Calmettes Institute, Marseille; ²Centre de Recherche sur le Cancer de Marseille (CRCM), Inserm U 1068; ³Aix-Marseille University, Marseille; ⁴Mixed Research Unit 912, Institute of Research and Development, National Institute of Health and Medical Research, Paoli Calmettes Institute, Aix-Marseille University, Marseille; ⁵Clinical Trial Office and Biostatistics Unit, Paoli Calmettes Institute, Marseille; ⁶Hematology Department, Haut-Leveque Hospital and Bordeaux University Hospital Center, Pessac; ⁷Hematology Department, University Hospital Center, Nantes; ⁸Hematology Department, University Hospital Center, Montpellier; ⁹Hematology Department, University Hospital Center, Lyon; ¹⁰Hematology Department, University Hospital Center, Clermont-Ferrand; ¹¹Hematology Department, University Hospital Center, Grenoble; ¹²CRNCA, UMR 892 INSERM - 6299 CNRS, and Université de Nantes, Faculté de Médecine, Nantes, France; and ¹³Hematology and Cellular Therapy Unit, AP-HP, Université Paris 6, Hôpital Saint Antoine, Paris, France

ABSTRACT

Allogeneic transplantation is a challenge in patients of advanced age because of a high risk of non-relapse mortality and potential long-lasting impairment of health-related quality of life. The development of reduced-intensity conditioning regimens has allowed the use of allogeneic transplantation in this population, but the optimal regimen remains undefined. We conducted a multicenter phase II trial evaluating the safety and efficacy of a reduced-intensity conditioning regimen combining fludarabine, intravenous busulfan, and rabbit antithymocyte globulins in patients older than 55 years of age transplanted from matched-related donor. In addition, health-related quality of life was prospectively measured. Seventy-five patients with a median age of 60 years (range 55-70) were analyzed. Grade III-IV acute and extensive chronic graft-versus-host diseases were found in 3% and 27% of patients, respectively. The day 100 and 1-year non-relapse mortality incidences were 1% and 9%, respectively. The cumulative incidences of relapse, progression-free survival and overall survival at two years were 36%, 51% and 67%, respectively, with a median follow up of 49 months. Global health-related quality of life, physical functioning, emotional functioning, and social functioning were not impaired compared to baseline for more than 75% of the patients (75%, 81.4%, 82.3%, and 75%, respectively). Thirty-four of the 46 (74%) progression-free patients at one year were living without persistent extensive chronic graft-versus-host disease. We conclude that the reduced-intensity conditioning regimen combining fludarabine, intravenous busulfan, and rabbit antithymocyte globulins is well tolerated in patients older than 55 years with low non-relapse mortality and long-term preserved quality of life. (*European Union Drug Regulating Authorities Clinical Trials, number 2005-005051-17*).

Introduction

Reduced-intensity conditioning (RIC) regimens allow for the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with advanced age and/or comorbidities who are classically not considered eligible for standard myeloablative allo-HSCT because of a high probability of non-relapse mortality (NRM). Various RIC regimens with different myeloablative intensities have been described but the optimal myeloablative intensity is still a matter of debate.¹⁻⁴ Truly non-myeloablative conditionings (NMAC) are intuitively preferred in the elderly because of the desirable low NRM. On the other hand, NMAC may ensure reduced antitumor activity, resulting in a higher relapse rate, particularly in patients with advanced or high-risk disease.⁵ Indeed, we previously reported that an RIC regimen combining fludarabine (Flu), intermediate dose of oral busulfan (Bu), and low-dose

rabbit thymoglobulin (r-ATG; Flu-Bu-r-ATG) delivered a better antitumor effect than a truly NMAC based on Flu and 2Gy total body irradiation (TBI). However, the Flu-Bu-r-ATG regimen led to an increase in morbidity and mortality, eventually resulting in similar overall outcomes.³ We later suggested that the use of intravenous Bu with an intermediate r-ATG dose could reduce the toxicity of RIC regimens without impairing disease control.^{6,7} With this background, we designed a prospective multicenter phase II trial evaluating the feasibility and efficacy of an RIC regimen combining Flu, intravenous Bu, and 5 mg/kg of r-ATG in patients over 55 years of age with hematologic malignancies.

Methods

Study design

This was a prospective multicenter study. The study protocol was

©2015 Ferrata Storti Foundation. This is an open-access paper. doi:10.3324/haematol.2014.113571

The online version of this article has a Supplementary Appendix.

Manuscript received on July 11, 2014. Manuscript accepted on November 20, 2014.

Correspondence: blaised@ipc.unicancer.fr

approved by each institutional review board at the eight participating institutions, the Marseille II Ethical Committee, and the Cellular Therapy Committee of the French Agency for the Safety of Health Products. Written informed consent in accordance with the Declaration of Helsinki was obtained from eligible patients and their donors prior to inclusion in the study. This trial was registered with the European Union Drug Regulating Authorities Clinical Trials, n. 2005-005051-17. Patients aged 55 years or over presenting with a hematologic malignancy for which an allo-HSCT was indicated, as previously described,⁸ were eligible if they had a matched related donor (MRD). The primary end point was the 1-year NRM cumulative incidence. Graft-versus-host disease (GvHD), relapse, progression-free survival (PFS), and overall survival (OS) were analyzed as secondary end points. Patients were enrolled in the study between March 2007 and May 2010.

Treatments

Conditioning regimen was a combination of Flu (Fludara; Schering AG, Lys-Les-Lannoy, France; 30 mg/m² daily on day -5 to day -1), intravenous Bu (Busilvex; Pierre Fabre, Boulogne-Billancourt, France; 0.8 mg/kg 4 times daily on days -4 and -3) and r-ATG (Thymoglobulin; Genzyme, St. Germain-en-Laye, France; 2.5 mg/kg daily, on days -2 and -1). Cyclosporine A, started on day -3, was used as GvHD prophylaxis. Supportive care, including anti-infectious drugs and blood product transfusions, was administered according to the usual policies of each center. Peripheral blood stem cells (PBSC) were harvested as previously described with a desired target of 4×10^6 CD34 cells per kg.³

Health-related quality of life study

Health-related quality of life (HRQL) was measured prospectively with the European Organization for Research and Treatment of Cancer Core (EORTC) Quality-of-Life Questionnaire-C30.⁹ The transplant patients received the questionnaire seven days prior to transplantation and on days 80, 180, and 360 after allo-HSCT. Patients who relapsed were excluded. Mean arithmetic of EORTC scores from the questionnaires carried out on day -7 and day +360 were compared using a Wilcoxon rank sum test. We also compared for each patient the absolute score at day +360 to the one performed on day -7 before allo-HSCT. We considered no impairment in HRQL if the absolute EORTC score at day +360 was at least equal to the one calculated at day -7 before allo-HSCT. As a surrogate marker of HRQL, we analyzed the prevalence of chronic GvHD (cGvHD) and immunosuppressive treatment (IST) at one year after allo-HSCT in progression-free patients.

Statistical analyses

To determine the optimal number of patients, a Fleming method at 1 step was used to detect a maximum NRM incidence of 25% at one year (considering reduction of 20% compared with the estimated 45% NRM for standard myeloablative regimens in this setting). With a *P* value of 0.01 and an alpha-risk of 90%, 74 patients were needed. Considering that 10% of included patients may eventually not be evaluable for the main objective, 82 patients were planned. We analyzed the cumulative incidences of acute GvHD (aGvHD) and cGvHD, as previously described.^{10,11} We analyzed NRM and relapse using Prentice estimation and the Gray test, taking into consideration competing events.^{12,13} Death without evidence of relapse was considered a competing event for the incidence of relapse. Similarly, the occurrence of relapse was considered a competing event for the incidence of NRM while relapse, progression, and deaths were treated as competing risks when analyzing the incidence of GvHD. PFS and OS were calculated using the Kaplan-Meier method, and results were compared

Table 1. Patients', disease and transplantation characteristics.

	All patients (n=75)	
	n	%
Age (years)		
Median [range]	60	[55-70]
Diagnosis		
AML	28	37%
MDS	14	19%
MM	12	16%
NHL	11	15%
CLL	5	7%
ALL	4	5%
CML	1	1%
Disease risk index ¹⁶		
Low	8	11%
Intermediate	53	72%
High	10	14%
Very high	2	3%
Unknown	2	
Karnofsky index		
90-100	48	72%
≤ 80	19	28%
Unknown	8	
HCT-CI ¹⁵		
0-2	26	36%
≥ 3	47	64%
Unknown	2	

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphoid leukemia; CML: chronic myeloid leukemia; CR: complete remission; HCTCI: hematopoietic cell transplantation comorbidity index; MDS: myelodysplastic syndrome; MM: multiple myeloma; NHL: non-Hodgkin lymphoma.

using the log rank test.¹⁴ We compared outcome of patients according to age (<60 vs. ≥60 years), Karnofsky performance status (KPS: 90-100 vs. <80), comorbidities using the hematopoietic cell transplantation comorbidity index (HCT-CI: 0-2 vs. ≥3),¹⁵ and the refined disease risk index (DRI) (low vs. intermediate vs. high/very high).¹⁶ All survival analyses were computed using R 3.1.0 statistical software (<http://www.R-project.org>).

Results

Patients' and transplant characteristics

Eighty-two patients were included in the study. Seven patients were excluded because of deviations in terms of the RIC regimen (n=5), of the donor (n=1), or the investigator's decision not to proceed to transplant (n=1). Median age of patients was 60 years; 13 patients were aged 65 years or older (Table 1). Patients were infused with a median of 4.9×10^6 CD34-positive cells/kg of body weight (range 0.7-17). Median follow up was 50 months (range 29-74).

Outcome after allo-HSCT

Overall outcomes after allo-HSCT are described in Table 2. NRM occurred at a median time of nine months (range 2-40) after allo-HSCT for a cumulative incidence of 1% and 9% on days 100 and 365, respectively (Figure 1A). We found significantly lower 5-year NRM in patients transplanted in good performance status (KPS: 90-100: 7% vs. ≤80: 26%; *P*=0.020) but no difference was observed

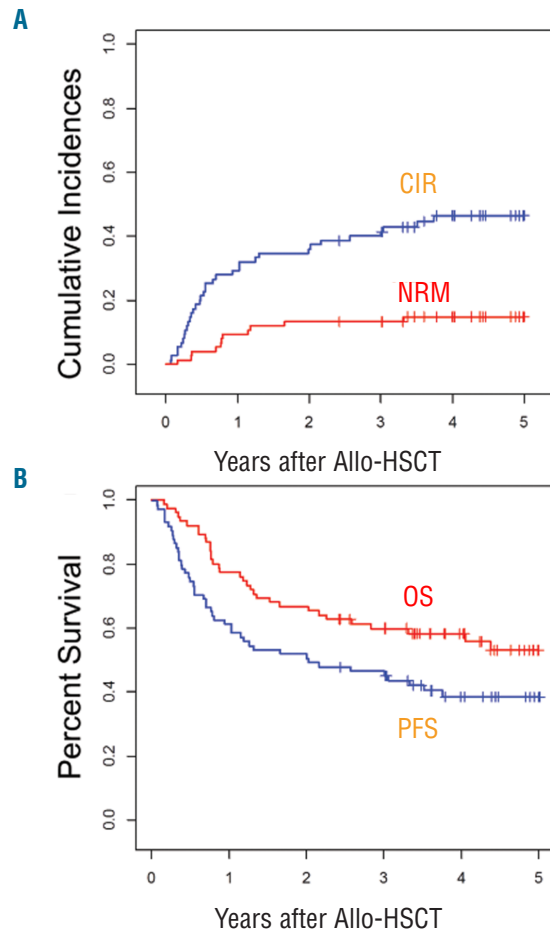


Figure 1. Outcome after allo-hematopoietic stem cell transplantation (HSCT). (A) Cumulative incidences of non-relapse mortality (NRM) and relapse (CIR). (B) Progression-free survival (PFS) and overall survival (OS) estimation.

according to age and/or HCT-CI (Table 3). The cumulative incidence of grade III-IV aGvHD and extensive cGvHD were 3% and 27%, respectively, irrespective of age. Thirty-four patients experienced disease relapse or progression at a median time of six months (range 1-45) for a 2-year cumulative incidence of 36% (95% confidence intervals: 25-45) (Figure 1A). Cumulative incidences of relapse after two years were 0%, 36% and 58% in patients with low, intermediate and high/very high DRI at the time of allo-HSCT, respectively ($P=0.307$). The main cause of death was disease recurrence (*Online Supplementary Table S1*). Two-year PFS and OS probabilities were 51% and 67%, respectively, with no significant differences according to age (Figure 1B). We found that DRI significantly predicted PFS and OS (Table 2 and Figure 2).

Patients with acute myeloid leukemia or myelodysplastic syndrome in first complete remission

Twenty-five patients were transplanted for acute myeloid leukemia (AML) ($n=20$) or myelodysplastic syndrome (MDS) ($n=5$), both in first complete remission (CR1). Fourteen (56%) were 60 years or older, 19 (76%) had an HCT-CI of three or more, and 8 (32%) had poor cytogenetics. Two-year cumulative incidence of relapse,

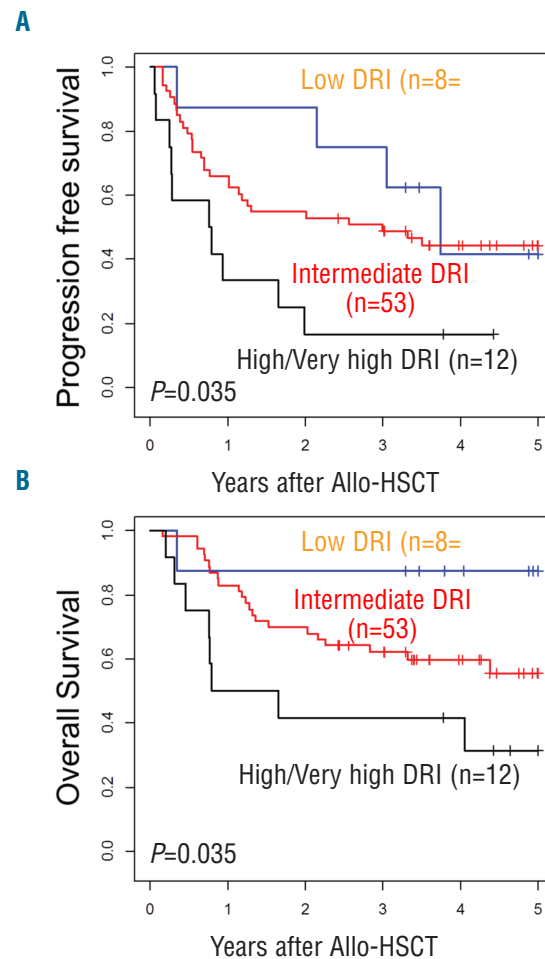


Figure 2. Outcome according to the revised disease risk index (DRI). (A) Progression-free survival (PFS). (B) Overall survival (OS).

PFS, and OS were 20%, 68% and 76%, respectively (*Online Supplementary Figure S1*). One year after allo-HSCT, 20 of 25 (80%) patients were alive and progression free. Among them, 18 (90%) were free of cGvHD, without IST ($n=15$) or with tapering IST ($n=3$). One patient (5%) was living with treated extensive cGvHD, and one patient (5%) was living with untreated limited cGvHD.

Health-related quality of life study

One year after allo-HSCT, 46 patients were alive and disease-free. We received 106 of the expected 184 questionnaires from these patients (58% reply rate). The descriptive analysis of the HRQL data revealed that the lowest functioning scores were experienced one month after allo-HSCT. Similar results were observed for the symptom scores. Thereafter, the level of symptoms decreased and levels of functioning increased and showed trends toward returning to day -7 before allo-HSCT levels. *Online Supplementary Figure S2* presents results for three functioning scales (physical functioning, cognitive functioning, and quality of life) and one symptom (fatigue). We performed a descriptive analysis of patients' answers based on patients completing both the first and last self-report questionnaires ($n=16$). One year after allo-HSCT,

global quality of life, physical functioning, emotional functioning, and social functioning were not impaired compared to day -7 before allo-HSCT for more than 75% of the patients (75%, 81.4%, 82.3%, and 75%, respectively) (Figure 3). Role functioning (38.9%) and cognitive functioning (28.8%) were the most impaired with a reduction in score one year after transplant. With regards to symptoms, pain and fatigue one year after transplant were not impaired for 81.3% and 70.6% of the patients, respectively. Of these 46 patients, 34 (74%) were living without cGvHD (30 without IST and 4 with tapering IST).

Discussion

We observed that an RIC regimen associating Flu, intravenous Bu, and an intermediate dose of r-ATG was well tolerated in patients 55 years of age or older undergoing allo-HSCT for hematologic malignancies. Indeed, we found a very low incidence of early NRM (1%), which is likely related to both low regimen-related toxicity and low

incidence of severe forms of aGvHD (grade III-IV: 3%). At a later stage, the incidence of NRM remained low (1-year: 9%; 5-year: 14%) with respect to median age (60 years; range 55-70) and high comorbidity score (hematopoietic cell transplantation specific-comorbidity index ≥ 3 : 64%). This promising safety profile is equivalent to that observed in patients receiving truly NMAC. Indeed, Storb *et al.* recently reported day 100, 1-year, and 5-year incidences of NRM of 4%, 15%, and 21%, respectively, in patients with a median age of 56 years (range 17-74) prepared with 2 Gy TBI +/- Flu.¹⁷ Taken together, these results show that this Flu-ivBU-ATG regimen delivers intermediate doses of myeloablation without increasing toxicity. The 53% OS at five years is also of interest with regards to the characteristics of the patient population: in addition to age and comorbidities, only 11% of the patients were considered to be low risk according to the refined DRI. The relapse rate remained relatively high with a 5-year PFS of 39%. However, when focusing only on the CR1 AML/MDS patients, we found a promising 2-year OS and PFS of 76% and 68%, respectively, with a

Table 2. Outcome after allo-HSCT.

	All patients (n=75)	
	%	(95%CI)
Acute GvHD		
Grade II-IV	21%	(12-31)
Grade III-IV	3%	(0-6)
Chronic GvHD		
Limited + Extensive	47%	(35-58)
Extensive	27%	(17-37)
Non-relapse mortality	14%	(7-23)
Incidence of relapse	46%	(35-58)
Progression-free survival	39%	(29-52)
Overall survival	53%	(42-65)
Follow up (months)		
Median [range]	49	[29-74]

Estimations are noted at 5 years except for acute graft-versus-host disease (aGvHD) that is estimated at day 100.

Table 3. Univariate analyses of non-relapse mortality and overall survival.

	N	NRM	P	OS	P
Age					
< 60 years	33	12%	0.650	61%	0.579
≥ 60 years	42	17%		45%	
Karnofsky index					
90-100	48	7%	0.020	42%	0.146
≤ 80	19	26%		56%	
HCT-CI ¹⁵					
0-2	26	20%	0.514	39%	0.094
≥ 3	47	13%		62%	
Disease risk index ¹⁶					
Low	8	13%	0.500	88%	0.041
Intermediate	53	9%		56%	
High / Very high	12	25%		31%	

HCTCI: hematopoietic cell transplantation comorbidity index; NRM: non-relapse mortality; OS: overall survival. Estimations are provided at 5 years.

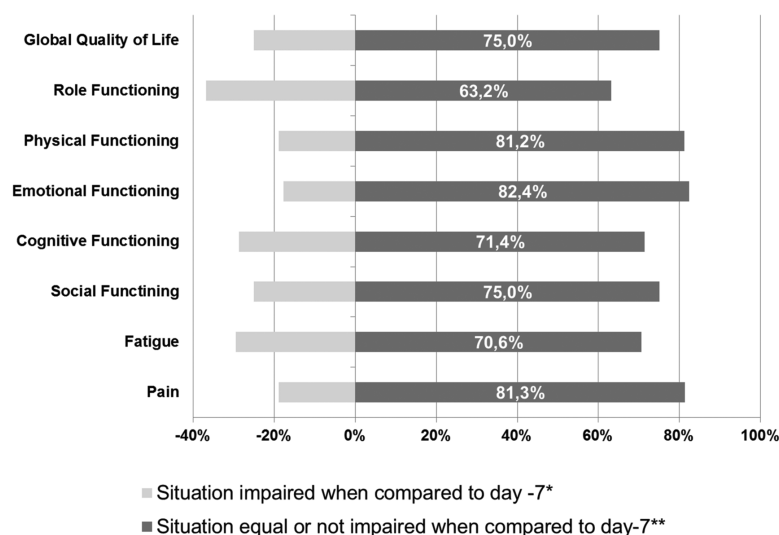


Figure 3. The proportion of patients reporting no impaired EORTC score one year after transplantation compared with base-line evaluation. *Score one year after transplantation is inferior to the day -7 score (pre-graft score). **Score one year after transplantation is superior or equal to the day -7 score (pre-graft score).

low incidence of relapse of 20%. The disease control achieved in patients with less advanced diseases is of interest and comparable to that observed with conditioning that were more intensive. Alatrash *et al.* recently reported 79 AML or MDS patients with a median age of 58 years (range 55-76) undergoing allo-HSCT prepared with 4-day intravenous Bu.¹⁸ When analyzing only the data from patients transplanted in CR1, they reported a 2-year OS and PFS of 71% and 68%, respectively, which is comparable to our results.

In addition to classical transplant outcomes, this clinical trial prospectively measured the HRQL in disease-free patients, which is a major issue, and one that is not frequently reported. Only 58% of the patients answered the HRQL study adequately. This rather low rate may be due to the age of the patient population studied; older patients are usually more reluctant to complete self-report questionnaires than younger patients.¹⁹ Due to the small sample size, one can argue that the statistical analyses used could not reflect the real population scores. To address this issue, we chose to perform a descriptive analysis of the proportion of patients whose EORTC scores returned to those of day -7 before allo-HSCT. This analysis provided encouraging results with a majority of patients describing EORTC scores that improved one year after transplant when compared to pre-transplantation scores. While poor quality of life is often presented as a limitation of allo-HSCT in older patients, our study suggested that, one year after transplantation, the majority of patients over 55 years of age had recovered standard of health outcomes similar to those recorded in the pre-transplant period. It is well known that cGvHD, particularly with refractory and/or recurrent extensive forms, is the main cause for changes in HRQL.^{20,21} In this series, 74% of the disease-free patients at one year after allo-HSCT were free of persisting cGvHD. The intermediate dose of r-ATG could, in part, explain these promising results. Indeed, we previously reported that the dose of r-ATG is critical for outcome after allo-HSCT, showing that an intermediate dose of 5 mg/kg results in effective GvHD prophylaxis while preserving disease control.^{22,23} The latter underlies the pivotal role of *in vivo* T-cell depletion even in the setting of MRD, which was recently confirmed in the large European Group for Blood and Marrow Transplantation study.²⁴ Overall, these results suggest that such RIC regimens could represent an optimal balance between safety and efficacy in a population of elderly patients transplanted from matched related donor. These results may differ when using unrelated donors. Alousi *et al.* reported that unrelated allo-HSCT were associated with higher incidences of GvHD and NRM in patients older than 50 years

of age.²⁵ In line with these data, we previously reported a 1-year NRM of 24% using the similar Flu-Bu-ATG platform in patients over 55 years of age receiving allo-HSCT from an unrelated donor compared to 9% in this present series.²⁶

Advanced diseases remain a major concern. Further developments to improve the antitumor effect of this Flu-ivBu-ATG platform are required. In this perspective, myeloablative regimens with reduced toxicity conditioning (MA-RTC) recently appeared as a valuable option in intermediate age patients combining both the low incidences of NRM from RIC regimens and the high antitumor effects from MAC.²⁷⁻²⁹ Furthermore, although in younger patients standard MAC may still play a role,³⁰⁻³² MA-RTC have been reported to be associated with lower incidences of GvHD and NRM but to a similar relapse rate in comparison to standard Bu plus cyclophosphamide MAC regimens, leading to improved outcomes.^{33,34}

Previous studies suggested that the dose of intravenous Bu could be safely increased in elderly patients with the aim of achieving better disease control in this setting in which standard MAC regimens are not an option.¹⁸ This hypothesis is currently being addressed in a French multicenter prospective clinical trial, where patients with high-risk myeloid malignancies will be randomized to receive different doses of intravenous Bu (6.4 vs. 9.6 vs. 12.8 mg/kg total dose).

In conclusion, we confirm that the current RIC regimen combining Flu, 2-day intravenous Bu, and 5mg/kg r-ATG resulted in reduced early toxicity and NRM, and interesting long-term preserved HRQL in elderly patients who underwent matched related allo-HSCT.

Acknowledgments

We thank the nursing staff under the supervision of L Caymaris for providing excellent care for our patients, and the following physicians for their dedicated patient care: C Oudin, R Crocchiolo, A Granata and C Faucher. We thank A Boyer-Chammard, MD, project leader in the clinical trial office for managing this study. We also thank the "Association pour la Recherche contre le Cancer".

Funding

Our group is supported by several grants from the French national cancer institute (PHRC INCa to M Mohty, N Milpied and D Blaise).

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

- Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood*. 1997;89(12):4531-4536.
- Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med*. 2005; 353(13):1321-1331.
- Blaise D, Tabrizi R, Boher J-M, et al. Randomized study of 2 reduced-intensity conditioning strategies for human leukocyte antigen-matched, related allogeneic peripheral blood stem cell transplantation: prospective clinical and socioeconomic evaluation. *Cancer*. 2013;119(3):602-611.
- Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood*. 1998;91(3):756-763.
- Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J Clin Oncol*. 2010; 28(17):2859-2867.
- Kashyap A, Wingard J, Cagnoni P, et al. Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem

- cell transplantation: decreased incidence of hepatic venoocclusive disease (HVOD), HVOD-related mortality, and overall 100-day mortality. *Biol Blood Marrow Transplant.* 2002;8(9):493-500.
7. Crocchiolo R, Esterni B, Castagna L, et al. Two days of antithymocyte globulin are associated with a reduced incidence of acute and chronic graft-versus-host disease in reduced-intensity conditioning transplantation for hematologic diseases. *Cancer.* 2013;119(5):986-992.
 8. Blaise D, Farnault L, Faucher C, et al. Reduced-intensity conditioning with Fludarabine, oral Busulfan, and thymoglobulin allows long-term disease control and low transplant-related mortality in patients with hematological malignancies. *Exp Hematol.* 2010;38(12):1241-1250.
 9. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.
 10. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation.* 1974;18(4):295-304.
 11. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med.* 1980;69(2):204-217.
 12. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94(446):496-509.
 13. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999;18(6):695-706.
 14. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457-481.
 15. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106(8):2912-2919.
 16. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood.* 2014;123(23):3664-3671.
 17. Storb R, Gyurkocza B, Storer BE, et al. Graft-versus-host disease and graft-versus-tumor effects after allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2013;31(12):1530-1538.
 18. Alatrash G, de Lima M, Hamerschlak N, et al. Myeloablative reduced-toxicity i.v. busulfan-fludarabine and allogeneic hematopoietic stem cell transplant for patients with acute myeloid leukemia or myelodysplastic syndrome in the sixth through eighth decades of life. *Biol Blood Marrow Transplant.* 2011;17(10):1490-1496.
 19. Pasetto LM, Falci C, Compostella A, Sinigaglia G, Rossi E, Monfardini S. Quality of life in elderly cancer patients. *Eur J Cancer.* 2007;43(10):1508-1513.
 20. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood.* 2006;108(8):2867-2873.
 21. Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood.* 2011;117(17):4651-4657.
 22. Devillier R, Fürst S, El-Cheikh J, et al. Antithymocyte globulin in reduced-intensity conditioning regimen allows a high disease-free survival exempt of long-term chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2014;20(3):370-374.
 23. Devillier R, Crocchiolo R, Castagna L, et al. The increase from 2.5 to 5 mg/kg of rabbit anti-thymocyte-globulin dose in reduced intensity conditioning reduces acute and chronic GVHD for patients with myeloid malignancies undergoing allo-SCT. *Bone Marrow Transplant.* 2012;47(5):639-645.
 24. Baron F, Labopin M, Blaise D, et al. Impact of in vivo T-cell depletion on outcome of AML patients in first CR given peripheral blood stem cells and reduced-intensity conditioning allo-SCT from a HLA-identical sibling donor: a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2014;49(3):389-396.
 25. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? *Blood.* 2013;121(13):2567-2573.
 26. Devillier R, Fürst S, Crocchiolo R, et al. A conditioning platform based on fludarabine, busulfan, and 2 days of rabbit antithymocyte globulin results in promising results in patients undergoing allogeneic transplantation from both matched and mismatched unrelated donor. *Am J Hematol.* 2014;89(1):83-87.
 27. De Lima M, Couriel D, Thall PF, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. *Blood.* 2004;104(3):857-864.
 28. Andersson BS, de Lima M, Thall PF, Madden T, Russell JA, Champlin RE. Reduced-toxicity conditioning therapy with allogeneic stem cell transplantation for acute leukemia. *Curr Opin Oncol.* 2009;21 Suppl 1:S11-5.
 29. Blaise D, Castagna L. Do different conditioning regimens really make a difference? *Hematology Am Soc Hematol Educ Program.* 2012;2012:237-245.
 30. Copelan EA, Hamilton BK, Avalos B, et al. Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI. *Blood.* 2013;122(24):3863-3870.
 31. Lee J-H, Joo Y-D, Kim H, et al. Randomized trial of myeloablative conditioning regimens: busulfan plus cyclophosphamide versus busulfan plus fludarabine. *J Clin Oncol.* 2013;31(6):701-709.
 32. Liu H, Zhai X, Song Z, et al. Busulfan plus fludarabine as a myeloablative conditioning regimen compared with busulfan plus cyclophosphamide for acute myeloid leukemia in first complete remission undergoing allogeneic hematopoietic stem cell transplantation: a prospective and multicenter study. *J Hematol Oncol.* 2013;6:15.
 33. Andersson BS, de Lima M, Thall PF, et al. Once daily i.v. busulfan and fludarabine (i.v. Bu-Flu) compares favorably with i.v. busulfan and cyclophosphamide (i.v. BuCy2) as pretransplant conditioning therapy in AML/MDS. *Biol Blood Marrow Transplant.* 2008;14(6):672-684.
 34. Chae YS, Sohn SK, Kim JG, et al. New myeloablative conditioning regimen with fludarabine and busulfan for allogeneic stem cell transplantation: comparison with BuCy2. *Bone Marrow Transplant.* 2007;40(6):541-547.