Reduced intensity conditioning for allogeneic haematopoietic stem cell transplantation (HSCT)

S. Servais, Y. Beguin, F. Baron

Reduced intensity conditioning (RIC) regimens have allowed performing allogeneic haematopoietic stem cell transplantation (HSCT) in patients for whom conventional myeloablative allogeneic HSCT is associated with unacceptable risks of non-relapse-mortality. This approach relies mainly on graft-versus-tumour effects for tumour eradication. Retrospective studies have suggested that, in patients aged 40 to 60 years, RIC-HSCT was associated with a higher risk of relapse but a lower incidence of transplant-related mortality than myeloablative allogeneic HSCT, leading to similar progression-free and overall survivals. After reviewing the rationale for RIC-HSCT, this article discusses the results of RIC-HSCT in specific diseases, and proposes what could be current indications for RIC-HSCT in 2011. Finally, the article briefly presents some possible strategies aimed at increasing the anti-tumoural activity of the procedure while reducing the incidence and severity of acute graft-versus-host disease.
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Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) following myeloablative conditioning has been an effective therapy for many patients with haematological diseases. However, myeloablative conditionings have been associated with significant morbidity and mortality, limiting their use to younger (<50 to 60 years of age) patients without medical comorbidities. This is unfortunate given that, in most cases, haematological malignancies are diagnosed in patients above 60 years of age.

Marrow failure (myeloablation) is the main complication of total body irradiation (TBI) and of many alkylating agents. The initial aim of allogeneic HSCT was to administer high doses of chemo-radiotherapy with the hope of eradicating as many malignant cells as possible, while marrows were infused to rescue patients from otherwise lethal marrow failure.[1] However, it was quickly recognised that the allograft itself conferred immune-mediated antileukaemic effects, termed graft-versus-tumour (GVT) effects. Evidence for GVT effects has included: 1) the observation that patients who developed graft-versus-host disease (GVHD) had lower risk of relapse than those who did not, 2) the higher risks of relapse observed in patients given T-cell depleted grafts and in those given grafts from identical twins, and 3) the ability of donor lymphocyte infusion to induce complete remissions (CR) in a number of patients in whom the haematological malignancy had relapsed after allogeneic HSCT.[2] It has been suggested that the main mechanisms of GVT effects were the recognition of

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host-specific minor or major histocompatibility antigens (and maybe tumour-specific antigens) by donor T cells, although several observations have also suggested a role for donor NK and B cells.[3-5]
The recognition of the importance of GVT effects in the eradication of malignant cells after myeloablative allogeneic HSCT led to the development of reduced-intensity (RIC) or truly nonmyeloablative conditioning regimens for allogeneic HSCT.
After reviewing the rationale for RIC-HSCT, this article discusses the results of RIC-HSCT in specific diseases, and proposes what could be current indications for RIC-HSCT in 2011. Finally, the article briefly presents some possible strategies aimed at increasing the anti-tumoural activity of the procedure while reducing the incidence and severity of acute GVHD.

Nonmyeloablative and reduced intensity conditioning regimens

Most RIC regimens combine fludarabine, with intermediate doses of alkylating agents such as busulfan, melphalan or thiothepa given with the objectives of preventing graft rejection (fludarabine) and controlling the malignancy (alkylating agents) before the occurrence of GVT effects (reviewed in[6]). Typical complications of high-dose therapy, such as mucositis, pancytopenia and organ damages can be observed with these regimens but have occurred less frequently after RIC than after myeloablative regimens. In contrast, nonmyeloablative regimens have relied on optimisation of pre- and post-transplant immunosuppression to allow engraftment, while eradication of tumours following nonmyeloablative conditioning has depended nearly exclusively on GVT effects. Typically, those regimens can be performed in the outpatient setting since myelosuppression is generally mild due to the co-existence of host-derived and donor-derived haematopoiesis during the first weeks (months) after HSCT.[7] The most frequently used nonmyeloablative conditionings include a combination of low-dose (2Gy) TBI with fludarabine and postgrafting immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP), and a combination of cyclophosphamide and fludarabine. Following nonmyeloablative conditioning, antitumour responses may require extended periods of time, with some patients achieving a CR more than one year after HSCT. Because of that, nonmyeloablative HSCT is generally not recommended for patients with aggressive malignancies not in good responses at the time of HSCT.
It has been suspected that RIC regimens might be associated with better survival than truly nonmyeloablative conditioning because of lower incidence of relapse and similar nonrelapse mortality. However, two recent studies have suggested that it might not be the case. Blaise et al. reported the results of a prospective randomised study comparing outcomes of 139 patients with haematological malignancies given grafts after fludarabine, busulfan (8 mg/kg) and ATG (n=69) or fludarabine and 2 Gy TBI (n=70).[8] With a median follow-up of four years, overall survival (the primary endpoint of the study) was similar in the two arms (44% versus 47%, respectively). Further, Mohty et al. compared outcomes of patients with acute myeloid leukaemia (AML) in first CR given grafts following low-dose TBI-based nonmyeloablative conditioning (n=323), versus more intense but still RIC regimen (n=877) in European group for Blood and Marrow Transplantation (EBMT)-affiliated centres.[9] Two year disease-free survival was similar in the two groups (50% versus 53%, respectively).

Graft-versus-host disease (GVHD)

A number of reports have compared the incidences of acute and chronic GVHD after nonmyeloablative/reduced-intensity conditioning or myeloablative allogeneic HCST. Most have shown lower incidences of acute GVHD (when acute GVHD was defined as GVHD occurring before day 100) but similar incidences of chronic GVHD with RIC or nonmyeloablative conditioning than with myeloablative conditioning. However, a number of patients given RIC or nonmyeloablative conditioning experienced late acute GVHD (i.e. acute GVHD occurring after day 100), often at the time of conversion from mixed to full donor T cell chimerism.[7] As mentioned earlier, occurrence of GVHD is strongly associated with graft-versus-tumour effects in patients given myeloablative conditioning. Since nonmyeloablative regimens rely nearly exclusively on GVT effects for tumour eradication, several groups of investigators looked at the impact of GVHD on HSCT outcomes after nonmyeloablative or RIC conditioning. The Seattle group analysed the impact of acute and chronic GVHD on HSCT outcomes in a cohort of 322 patients given nonmyeloablative HSCT as treatment for various haematological malignancies.[10] Grade II and grade III-IV acute GVHD were not significantly associated with lower risks of progression/

Table 1. Retrospective studies comparing haematopoietic stem cell transplantation (HSCT) outcomes of patients given grafts after nonmyeloablative/reduced intensity conditioning (RIC) or myeloablative conditioning.

Authors (reference)	Disease	Relapse (HR (95%CI); P value)	Nonrelapse mortality (HR (95%CI), P value)	Progression-free survival (HR (95%CI), P value)
Aoudjhane[14]	AML	1.78 (1.3-2.43); 0.0003	0.48 (0.33-0.68); <0.001	1.15 (0.9-1.47); 0.24
Martino[15]	MDS	1.64 (1.2-2.2); 0.001	0.61 (0.41- 0.91); 0.015	1.1 (0.8-1.4); 0.9
Dreger[16]	CLL	2.46 (0.9-6.72); 0.08	0.4 (0.18-0.9); 0.03	0.69 (0.38-1.25); 0.22

AML=acute myeloid leukaemia, MDS=myelodysplastic syndrome, CLL=chronic lymphocytic leukaemia, HR=hazard ratio.

relapse, but were instead associated with increased nonrelapse mortality and lower progression-free survival. In contrast, occurrence of chronic GVHD correlated with lower risks of relapse in multivariate time-dependent analyses (HR=0.4, P=0.006) and was associated with significantly better progression-free survival (HR=0.5, P=0.003). Similar observations were recently reported by Thepot et al.[11]

Attempts at further reducing GVHD after RIC/nonmyeloablative conditioning by performing in vivo T-cell depletion by ATG or alemtuzumab have achieved their goal but have been associated with higher risk of relapse.[12] Another approach aimed at reducing the incidence of acute GVHD has been developed by the Stanford University group. Based on murine experiments, the authors investigated a novel nonmyeloablative regimen that favoured the presence of a high proportion of regulatory NK-T cells.[13] This regimen consisted of TLI (8 Gy) and ATG (Thymoglobulin, 7.5 mg/kg total dose), and postgrafting immunosuppression with MMF and CSP. First results in 110 patients with various haematological malignancies indicated that this regimen was indeed associated with a low incidence of grade II-IV acute GVHD (<10%), while GVT effects were apparently preserved.[14]

Comparison of results with myeloablative or RIC regimens

Three large retrospective studies from the EBMT have compared HSCT outcomes of patients given various myeloablative versus various RIC/nonmyeloablative regimens as treatment for AML, MDS, or chronic lymphocytic leukaemia (CLL) (*Table 1*).[14-16] Obviously these studies are limited by the fact that fitter patients were probably more often proposed myeloablative regimens, while older and sicker patients were probably more often given nonmyeloablative or RIC regimens. Nevertheless, these studies found similar disease-free and overall survivals in the 2 groups of patients, since nonrelapse mortality was lower in nonmyeloablative patients, but relapse rate was lower in myeloablative recipients.[14-16]

Results in specific diseases

Acute leukaemias

The susceptibility of the different groups of haematological malignancies to graft-versus-tumour effects is supposed to be different (*Figure 1*). The largest prospective study of nonmyeloablative HSCT as treatment for AML has been recently reported by the Seattle consortium.[17] 274 patients with AML in first (n=160) or second (n=71) CR or with more advanced diseases (n=43) were included. Conditioning regimen consisted of fludarabine and 2 Gy TBI. Five-year overall survival was 37% for patients in first CR at the time of HSCT, 34% for those in second CR and 18% for those with more advanced disease. Other factors associated with survival included cytogenetic risks (5-year overall survival of 40% for patients with good/intermediate cytogenetics versus 19% for those with poor risk cytogenetics, and chronic GVHD who was associated with better survival in time-dependent analysis (HR 0.7, P=0.07, due to a 2 time reduction in the risk of relapse (P=0.01)). These observations suggest that RIC-HSCT could be a routine indication for older but fit patients with poor or intermediate cytogenetic/molecular risk AML in first CR and for those with AML in second CR (*Table 2*, page 6). A large randomised study is on the way among EBMT-affiliated centres to evaluate the impact of RIC-HSCT on disease-free survival in patients with AML in first CR.

Nonmyeloablative or RIC HSCT are also increasingly used as treatment for patients with acute lymphoblastic leukaemia (ALL). Interestingly preliminary data from 2 retrospective studies (1 from the CIBMTR and 1 from the EBMT) have showed similar survival in ALL patients given RIC/nonmyeloablative condi-

Table 2. Potential current indications for nonmyeloablative / reduced intensity conditioning (RIC) in patients ineligible for myeloablative allogeneic haematopoietic stem cell transplantation (HSCT).

Disease	Type of indication
Acute myeloid leukaemia	
first CR high or intermediate molecular/cytogenetic risk	routine
first CR low molecular/cytogenetic risk	not recommended
second CR	routine
not in CR	not recommended
Acute lymphoblastic leukaemia	
in CR	CRP
not in CR	not recommended
Myelodysplastic syndrome	
IPSS ≤1.0	not recommended
IPSS >1.0 with <5% marrow blasts at HSCT	routine
>5% marrow blasts at HSCT	not recommended
Advanced myelofibrosis	routine
High-grade B cell lymphoma	
CR1	not recommended*
PR1	CRP
CR2 not eligible for autologous HSCT	CRP
sensitive relapse after autologous HSCT	routine
refractory to chemotherapy	not recommended
Low-grade B cell lymphoma	
CR1 or CR2	not recommended
relapse after autologous HSCT	routine
advanced and ineligible for autologous HSCT	CRP
Mantle cell lymphoma	
CR1 ineligible for autologous HSCT	CRP
CR2 or sensitive relapse	routine
refractory to chemotherapy	not recommended
T cell lymphoma	
sensitive disease	CRP
refractory disease	not recommended
Hodgkin disease	
sensitive relapse after autologous HSCT	CRP
refractory to chemotherapy	not recommended
Chronic lymphocytic leukaemia	
sensitive to fludarabine	not recommended
fludarabine refractory** but without bulky disease	routine
fludarabine refractory** with bulky disease at HSCT	not recommended
P53 mutation / deletion (del 17p13) requiring treatment without bulky disease	routine
Multiple myeloma (first line or at relapse)	CRP

*CR=complete remission, routine=in routine use for selected patients (level of evidence-based medicine 3 or 4), CRP=to be undertaken in approved Clinical Research Protocols, not recommended=not generally recommended, *CRP for patients with aaIPI 2-3 at diagnosis in CR1 ineligible for autologous HSCT but fit for RIC-HSCT, **defined as non-response or early relapse (within 12 months) after purine analogue-containing therapy, relapse (within 24 months) after purine analogue combination therapy or treatment of similar efficacy (i.e., autologous HSCT).*

tioning in comparison to those given myeloablative conditioning.[18] These encouraging data confirm the existence of graft-versus-ALL effects and might serve as rationale for the design of large prospective studies from leukaemia collaborative groups evaluating the role of RIC-HSCT in patients high-risk ALL.

Myelodysplastic syndrome and myeloproliferative disorders

Martino et al. reported the outcomes of 215 patients given one of various RIC or nonmyeloablative conditioning as treatment for MDS (refractory anaemia (n20) or more advanced MDS (n=195)) among EBMT-affiliated centres.[15] Three-year incidences of relapse and nonrelapse mortality were 45 and 22%, respectively, while 3-year overall survival was 41%. These results seem to be better than those reported by Laport et al. in patients with MDS given grafts after 2 Gy TBI plus fludarabine (3-year overall survival of 27%), perhaps due to a high incidence of graft rejection among previously untreated patients given low-intensity nonmyeloablative conditioning.[19]

More recently, Kroger et al. reported the results of a prospective study of RIC allogeneic HSCT as treatment for patients with myelofibrosis.[20] 103 patients were includ-

ed. The conditioning regimen consisted of busulfan (10 mg/kg), fludarabine and ATG. Five-year incidence of relapse was 22%, while 5-year progression-free and overall survivals were 51 and 67%, respectively.

Since allogeneic transplantation is the only potentially curative treatment for MDS and myelofibrosis, RIC-HSCT might be considered as a routine approach for older but fit patients suffering from advanced MDS or advanced myelofibrosis with <5% marrow blasts at HSCT. Given the high incidence of graft rejection with truly nonmyeloablative conditioning regimen in patient not given any chemotherapy before the conditioning regimen for HSCT, it might be reasonable to prefer a busulfan-based RIC to a truly nonmyeloablative regimen in patient with MDS or myelofibrosis not given intensive chemotherapy before transplantation.[7]

Lymphomas

A number of studies have evaluated HSCT following reduced-intensity or nonmyeloablative conditioning regimens as treatment for patients with advanced lymphoma, including those relapsing after autologous HSCT.[21-23] Graft-versus-tumour effects were particularly impressive in patients with indolent or mantle-cell lymphomas, as well as in those with chemosensitive aggressive lymphomas.[24] Further, two recent reports recently demonstrated that some patients with Hodgkin lymphoma relapsing after autologous HSCT could be salvaged with nonmyeloablative/RIC allo-HSCT.[21,23] In our opinion, routine indications for RIC-HSCT in patients with lymphoma might include patients with sensitive relapse after autologous HSCT, and patients with mantle cell lymphoma with sensitive relapse or second CR.

Chronic lymphocytic leukaemia

Sorror et al. described outcomes in 82 patients (median age 56 years) with fludarabine-refractory CLL who received HSCT from HLA-matched related (n=52) or unrelated (n=30) donors after conditioning with 2 Gy TBI alone or combined with fludarabine.[25] With a median follow-up of 5 years, 5-year rates of relapse and nonrelapse mortality were 38% and 23%, respectively, while 5-year overall survival was 50%. These results demonstrate that CLL is remarkably susceptible to GVT effects, and that a significant proportion of patients with fludarabine-refractory CLL might be cured by RIC/nonmyeloablative HSCT. According to the EBMT, RIC-HSCT is a standard treatment for eligible patients with previously treated, poor-risk CLL (defined as non-response or early relapse (within 12 months) after purine analogue-containing therapy; relapse (within 24 months) after purine analogue combination therapy or treatment of similar efficacy (i.e., autologous HSCT); p53 deletion/mutation (del 17p13) requiring treatment).[26]

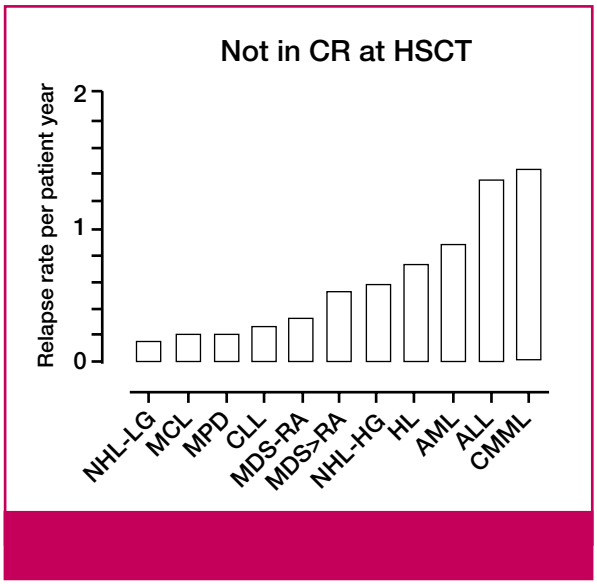

Figure 1. Susceptibility of disease groups to graft-versus-tumour effects. Relapse rates per patient year during the first 2 years after haematopoietic stem cell transplantation (HSCT) corrected for follow-up and competing nonrelapse mortality in patients reported in ref. 24 given grafts after 2 Gy total body irradiation with or without added fludarabine not in complete remission (CR) at HSCT. NHL-LG=low-grade non-Hodgkin lymphoma, MCL=mantle cell lymphoma, MPD=myeloproliferative disease, CLL=chronic lymphocytic leukaemia, MDS-RA=myelodysplastic syndrome in refractory anaemia, NHL-HG=high-grade NHL, HL=Hodgkin lymphoma, AML=acute myeloid leukaemia, ALL=acute lymphoblastic leukaemia, CMML=chronic myelomonocytic leukaemia.

Multiple myeloma

The role of nonmyeloablative HSCT in patients with multiple myeloma has been controversial. The Intergroupe Francophone du Myélome compared the outcomes of 284 patients with high risk multiple myeloma treated in two separate prospective protocols consisting of either double autologous HSCT or single autologous HSCT followed by RIC allogeneic HSCT.[27] Survival was worse in the autologous/allogeneic arm but this might be due to the fact that allografting was preceded by administration of high-doses of ATG that might have abrogated the graft-versus-myeloma effects. Bruno et al. compared a protocol that entailed an autologous HSCT followed by an allograft from an HLA-

Key messages for clinical practice

1. **Allogeneic haematopoietic stem cell transplantation (HSCT) following reduced intensity conditioning (RIC) or truly nonmyeloablative conditioning regimen is a potentially curative option for patients with haematological malignancies ineligible for high-dose conditioning regimen.**

2. **Current potential indications for patients with myeloid malignancies include high-risk acute leukaemia in complete remission, high-risk MDS with <5% marrow blasts at HSCT, and advanced myeloproliferative disorders not in blastic phase.**

3. **Current indications for patients with lymphoid malignancies include chemosensitive high-grade non-Hodgkin lymphoma relapsing after autologous HSCT, chemosensitive Hodgkin lymphoma relapsing after autologous HSCT, advanced low-grade non-Hodgkin lymphoma, mantle cell lymphoma, and fludarabine-refractory CLL.**

4. **Allogeneic HSCT following RIC or truly nonmyeloablative conditioning should preferably be performed in clinical trials.**

identical sibling (following conditioning with 2 Gy TBI as conditioning regimen) for all patients with a HLA-identical sibling with a protocol of tandem autologous HSCT for patients without a HLA-identical sibling.[28] After a median follow-up of 45 months, the median overall survival and event-free survival were longer in the 80 patients with HLA-identical siblings than in the 82 patients without HLA-identical siblings (80 months versus 54 months, P=0.01; and 35 months versus 29 months, P=0.02, respectively). Similar results have been reported in an EBMT-sponsored prospective trial using similar conditioning to autologous and allogeneic HSCT (Gahrton et al., oral communication at the 2009 EBMT general meeting). Results of the large ongoing CIBMTR study assessing the role of tandem autologous/allogeneic HSCT in patients with multiple myeloma will help to better define the role of RIC-HSCT in patients with multiple myeloma.

Conclusions and Perspectives

Allogeneic HSCT following RIC or truly nonmyeloablative conditioning regimens has allowed curing many patients with otherwise fatal haematological malignancies. Potential current indications for nonmyeloablative / reduced intensity conditioning (RIC) in patients ineligible for myeloablative allogeneic haematopoietic stem cell transplantation (HSCT) are summarised in *Table 2*. Current researches are aimed at decreasing the incidence of acute GVHD (that has not been associated with GVT effects after nonmyeloablative conditioning), at improving immune recovery after HSCT, and at further increasing the anti-cancer activity of the procedures.[29] Potential strategies to decrease the incidence of acute GVHD are investigating novel postgrafting immunosuppression strategies as well as the use of immuno-regulatory cells such as NK/T cells, mesenchymal stem cells, or regulatory T cells.[13,30] Potential strategies aimed at increasing GVT effects are investigating combining RIC/nonmyeloablative conditioning with pre- or post-transplant disease-targeted therapy such as imatinib, thalidomide, bortezomib, rituximab, azacytidine, or radiolabeled monoclonal antibodies.

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References

1. Little M-T, Storb R. History of haematopoietic stem-cell transplantation. Nature Reviews Cancer 2002;2:231-8.

2. Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. Blood 2008;112:4371-83.

3. Baron F, Petersdorf EW, Gooley T, et al. What is the role for donor natural killer cells after nonmyeloablative conditioning? Biol Blood Marrow Transplant 2009;15:580-8.

4. Verheyden S, Schots R, Duquet W, et al. A defined donor activating natural killer cell receptor genotype protects against leukemic relapse after related HLA-identical hematopoietic stem cell transplantation. Leukemia 2005;19:1446-51.

5. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood 2005;105:2973-8.

6. Baron F, Sandmaier BM. Nonmyeloablative Transplantation. In: Soiffer RJ, editor. Hematopoietic Stem Cell Transplantation. Totowa: Humana Press, 2008:349-74.

7. Baron F, Baker JE, Storb R, et al. Kinetics of engraftment in patients with hematologic malignancies given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. Blood 2004;104:2254-62.

8. Blaise D, Tabrizi R, Le Corroller AG, et al. Prospective Randomized Comparison of Reduced Intensity (FLU-BU-ATG) and Non-Myeloablative (FLU-TBI) Conditioning for Genoidentical Allo-SCT: a Clinical and economical Multicenter Itac Study. ASH Annual Meeting Abstracts 2009;114:193.

9. Mohty M, Labopin M, Janssen JJ, et al. Comparison of Low Dose Total Body Irradiation (TBI)-Based Reduced Intensity Conditioning (RIC) Vs. Chemotherapy-Based RIC Prior to Allogeneic Stem Cell Transplantation (allo-SCT) From An HLA Identical Sibling Donor for Acute Myeloid Leukemia (AML) in First Complete Remission (CR1): a Retrospective Analysis of 1200 Patients From the Acute Leukemia Working Party of EBMT. ASH Annual Meeting Abstracts 2009;114:1190.

10. Baron F, Maris MB, Sandmaier BM, et al. Graft-versus-tumor effects after allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning. J Clin Oncol 2005;23:1993-2003.

11. Thepot S, Zhou J, Perrot A, et al. The graft-versus-leukemia effect is mainly restricted to NIH-defined chronic graft-versus-host disease after reduced intensity conditioning before allogeneic stem cell transplantation. Leukemia 2010;24:1852-8.

12. Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood 2005;105:4532-9.

13. Kohrt HE, Turnbull BB, Heydari K, et al. TLI and ATG conditioning with low risk of graft-versus-host disease retains antitumor reactions after allogeneic hematopoietic cell transplantation from related and unrelated donors. Blood 2009;114:1099-109.

14. Aoudjhane M, Labopin M, Gorin NC, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Leukemia 2005;19:2304-12.

15. Martino R, Iacobelli S, Brand R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood 2006;108:836-46.

16. Dreger P, Brand R, Milligan D, et al. Reduced-intensity conditioning lowers treatment-related mortality of allogeneic stem cell transplantation for chronic lymphocytic leukemia: a population-matched analysis. Leukemia 2005;19:1029-33.

17. Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. J Clin Oncol 2010;28:2859-67.

18. Marks DI, Wang T, Perez WS, ,et al. Comparison of Outcomes for Non-Myeloablative (NMA) and Myeloablative (MA) Conditioning for Adults with Acute Lymphoblastic Leukaemia (ALL) in First and Second Complete Remission (CR): a Center for International Blood and Marrow Transplant Research (CIBMTR) Analyisis. ASH Annual Meeting Abstracts 2009;114:872.

19. Laport GG, Sandmaier BM, Storer BE, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. Biol Blood Marrow Transplant 2008;14:246-55.

20. Kroger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood 2009;114:5264-70.

21. Robinson SP, Sureda A, Canals C, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome. Haematologica 2009;94:230-8.

22. Escalon MP, Champlin RE, Saliba RM, et al. Nonmyeloablative allogeneic hematopoietic transplantation: a promising salvage therapy for patients with non-Hodgkin's lymphoma whose disease has failed a prior autologous transplantation. J Clin Oncol 2004;22:2419-23.

23. Baron F, Storb R, Storer BE, et al. Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation. J Clin Oncol 2006;24:4150-7.

24. Kahl C, Storer BE, Sandmaier BM, et al. Relapse risk in patients with malignant diseases given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. Blood 2007;110:2744-8.

25. Sorror ML, Storer BE, Maloney DG, et al. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. Blood 2008;111:446-52.

26. Dreger P, Corradini P, Kimby E, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia 2007;21:12-7.

27. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474-80.

28. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007;356:1110-20.

29. Castermans E, Hannon M, Dutrieux J, et al. Thymic recovery after allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning is limited to patients younger than 60 years of age. Haematologica 2011;96:298-306.

30. Baron F, Lechanteur C, Willems E, et al. Cotransplantation of mesenchymal stem cells might prevent death from graft-versus-host disease (GVHD) without abrogating graft-versus-tumor effects after HLA-mismatched allogeneic transplantation following nonmyeloablative conditioning. Biol Blood Marrow Transplant 2010;16:838-47.