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Hematopoietic Stem Cell Transplantation after Reduced Intensity Conditioning in Acute Myelogenous Leukemia Patients Older Than 40 Years

Cynthia Huisman, Ellen Meijer, Eefke J. Petersen, Henk M. Lokhorst, Leo F. Verdonck

Department of Hematology, University Medical Center, Utrecht, The Netherlands

Correspondence and reprint requests: Cynthia Huisman, MD, PhD, Department of Hematology, B02.226, University Medical Center Utrecht, Heidelberglaan 100 3584 CX Utrecht, The Netherlands (e-mail: c.huisman@tiscali.nl).

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ABSTRACT

Reduced intensity conditioning (RIC) protocols are increasingly used for allogeneic hematopoietic stem cell transplantation (HSCT) in elderly patients. We analyzed the outcome of RIC HSCT in acute myelogenous leukemia (AML) patients over the age of 40 years. Forty-three AML or high-risk myelodysplastic syndrome (MDS) patients were treated with a fludarabine and low-dose total-body irradiation (TBI)-based pretransplantation regimen. Donors were HLA-compatible sibling (68%) or unrelated volunteers (34%). All but 2 AML patients were in complete remission (CR) at the time of transplantation. Seventy-six percent of patients had a poor risk profile. Hematologic recovery was fast, and primary graft failure occurred in 1 patient. Two patients with active disease at the time of HSCT experienced ongoing relapse. Infections were diagnosed in 9 patients (21%), and 6 patients (14%) were treated for cytomegalovirus (CMV) reactivation. Sixty percent of patients developed acute graft-versus-host disease (aGVHD), which was grade II in 40% and grade III in 12%. The cumulative incidence of chronic graft-versus-host disease (cGVHD) was 33% at 1 and at 2 years. Treatment-related mortality (TRM) was low (9%), total nonrelapse mortality (NRM) was 19%. After a median follow-up of 571 days, 16 patients (37%) experienced relapse. Median disease-free and overall survival (DFS; OS) were 24 and 31 months, respectively. There were no differences in complications and outcome between recipients of sibling and unrelated grafts. In conclusion, fludarabine plus low-dose TBI-based RIC HSCT is effective in AML patients over the age of 40 years without active disease at the time of transplant and is associated with low TRM.

KEY WORDS

Acute myelogenous leukemia • Reduced intensity conditioning • Stem cell transplantation

INTRODUCTION

The major cause of death in patients with acute myelogenous leukemia (AML) is relapse. Intensive postremission therapy is indicated to obtain durable responses. However, the majority of AML patients is older than 60 years of age, and intensive chemotherapy alone is unlikely to cure this group [1].

For many patients allogeneic hematopoietic stem cell transplantation (HSCT) offers the highest curative potential. Since the introduction of reduced intensity conditioning (RIC) protocols, elderly patients and those with high risk of treatment-related mortality (TRM) have increasingly become eligible for allogeneic HSCT. RIC regimens rely on the graft-versus-leukemia (GVL) effect for disease eradication. Evidence for a GVL effect in AML has been established by observations that patients experiencing graft-versus-host disease (GVHD) have an increased progression-free survival (PFS) [2] and the capability of donor lymphocyte infusions (DLI) to introduce complete remissions (CR) in some AML patients relapsing after HSCT [3].

Several RIC protocols are being used, varying from moderately myelotoxic to truly nonmyeloablative (for reviews see [4-7]). Some retrospective studies in AML patients demonstrated that RIC results in less transplant toxicity but more relapses than more intensive pretransplant regimens [8,9]. Others, however, did not find a better disease outcome after myeloablative conditioning [10,11]. A donor versus no-donor comparison of RIC HSCT in AML showed increased leukemia-free and overall survival (OS) for the

transplant group in high-risk patients over the age of 50 years or with significant comorbidity [12]. Another study demonstrated superior outcome after RIC HSCT compared to chemotherapy in patients 50 years or older in CR1 [13].

Until now, no prospective randomized trials comparing myeloablative conditioning with RIC in AML patients were available, and important issues regarding the optimal RIC regimen, age limits of selected patients, and timing of the RIC HSCT [14] are still unanswered. The current analysis adds to the still limited evidence of single-arm phase 2 studies reporting the results of RIC HSCT in a homogeneous group of AML patients over the age of 40 years.

PATIENTS AND METHODS

Patients

This retrospective analysis describes 43 consecutive patients with AML or high-risk myelodysplastic syndrome (MDS) ≥40 years of age who received an allogeneic RIC peripheral blood HSCT at our institution between February 2002 and July 2006. One patient aged 27 was included in this group because of a previous autologous SCT. Twenty-seven AML patients had received induction therapy according to HOVON 42 and 43 protocols with idarubicin or daunorubicin plus cytarabine, followed by at least 1 consolidation course consisting of high-dose cytarabine. Different regimens were applied in 2 patients. Eleven patients were treated because of relapse AML with high-dose cytarabine (3000 mg/m^2 twice a day for 6 days) before HSCT. Three MDS patients did not receive any previous therapy. All but 2 AML patients were in CR at the time of transplantation.

Patient characteristics are shown in Table 1. Cytogenetics were grouped as good (inv[16], t[8;21], and t[15;17]), poor (−5, −7, 11q23, and complex karyotype), or intermediate (all others). High-risk leukemia included CR >1, secondary leukemia from an antecedent hematologic disorder, or poor cytogenetics. All patients were ≥5/6 matched with their donor at HLA -A, -B, and -DR by serologic testing in case of a sibling donor and ≥9/10 matched at HLA -A, -B, -C, -DR, and -DQ by high-resolution typing for unrelated donors.

Table 1. *Patient Characteristics*

Characteristics	
Total no. of patients	**43**
Male	**24 (56%)**
Female	**19 (44%)**
Age, years	
Median	**58**
Range	**27-69**
Diagnosis	
Acute myelogenous leukemia	**36 (84%)**
Myelodysplastic syndrome	**7 (16%)**
Cytogenetic risk group	
Good	**2 (5%)**
Intermediate	**29 (67%)**
Poor	**12 (28%)**
Leukemic risk	
Standard	**14 (33%)**
High	**29 (67%)**
Type of donor	
Sibling	**28 (66%)**
Matched unrelated	**15 (34%)**
No. of HLA-mismatch	
0	**38 (88%)**
1	**5 (12%)**
Previous SCT	
Autologous	**1 (2%)**
Allogeneic	**1 (2%)**

For definitions, see Patients and Methods; SCT indicates stem cell transplantation.

Transplantation Procedure

The conditioning regimen consisted of fludarabine 30 mg/m^2 for 3 days followed by 1 course of low-dose total-body irradiation (TBI) (200 cGy), according to the regimen developed by the Seattle group [15,16] and a full non-T cell-depleted PBSC graft. Antithymocyte globulin (ATG; Thymoglobulin^{TM}, Genzyme) was given to the 15 matched unrelated donor (MUD) patients before fludarabine was infused, at a dose of 2 mg/kg/day for 4 days.

Infection prevention consisted of ciprofloxacin and fluconazole until granulocyte counts exceeded 0.5 × 10^9/L. Furthermore, cotrimoxazole and valacyclovir were given orally from day +1 until 12 months posttransplantation or longer in the case of active GVHD, in a dose of 480 mg twice a day and 500 mg twice a day, respectively. Cytomegalovirus (CMV)-seropositive patient/donor combinations were monitored once a week during the first 120 days posttransplant by CMV DNA PCR. Preemptive treatment with ganciclovir was started when tests became positive.

Chimerism analysis was performed in T and non-T cell fractions by PCR-based amplification of short tandem repeat sequences. Peripheral blood samples were scheduled at monthly intervals post-SCT until complete chimerism was demonstrated twice. DLI was administered in case of (pending) relapse at a dose of 0.01 to 1.0 × 10^8 T cells/kg.

GVHD

Posttransplant immunosuppression consisted of cyclosporin (4.5 mg/kg twice a day) in combination with mycophenolate mofetil (MMF; 30 mg/kg/day). In the absence of active GVHD, MMF was tapered at 3 months posttransplant. In case no GVHD developed, dose reduction of cyclosporin started 2 weeks after, MMF was stopped. GVHD was diagnosed according to the Seattle criteria [17] and treated with

1 to 2 mg/kg/day prednisolone and resumption of full-dose immunosuppression if applicable.

Statistical Methods

OS and disease-free survival (DFS) were estimated by Kaplan-Meier analysis. OS was calculated from the day of SCT death or last follow-up. DFS was calculated from the day of SCT until relapse, death, or last follow-up. Patient characteristics were compared by the χ^2 test or Fisher exact test for categoric variables and the t-test for continuous variables. Univariate and multivariate analyses of risk factors were performed by logistic regression. The incidence of chronic GVHD (cGVHD) and relapse were estimated by cumulative incidence analysis considering death as competing event. Death from relapse was considered as a competing event to calculate the cumulative probability of total nonrelapse mortality. For all tests, a 2-sided P-value of ≤.05 was considered statistically significant. Calculations were performed using SPSS/PC+ 15.0 (SPSS Inc., Chicago IL).

RESULTS

Engraftment and Chimerism

Hematologic recovery was fast in nearly all patients. Two patients received HSCT while not in remission and experienced ongoing relapse requiring multiple transfusions with red blood cells and platelets. Primary graft failure occurred in 1 patient (2%). Therefore, 40 patients could be evaluated for engraftment and chimerism.

In 29 patients (73%) neutrophils decreased to $<0.5 \times 10^9$/L and recovered at a median of 19 days (range: 8-29 days) after transplantation. Twenty-three percent of patients developed a platelet count $<20 \times 10^9$/L for a median duration of 10 days (range: 7-14 days). The incidence of neutropenia was similar in recipients of sibling and MUD transplants (71% versus 75%, $P = .82$) but the duration of neutropenia was longer in the MUD group (median 16 versus 22 days, $P = .001$). Thrombocytopenia occurred in 14% of sibling and 42% of MUD HSCT ($P = .06$), and was present at a median of 10 days in both groups ($P = .73$). The differences in incidence of thrombocytopenia and duration of neutropenia between recipients of sibling and MUD grafts are probably caused by the addition of ATG in the MUD group. Red blood cell transfusions were necessary in 14 of 40 patients (35%), whereas platelet transfusions were administered to 7 patients (18%).

Chimerism analysis could be performed in 80% of patients at day +28 and demonstrated a median of 80% and 96% of donor cells in the T cell and non-T cell fraction, respectively. At +3 months, these numbers were 86% and 88%, respectively, in 32 of 40 (83%) evaluable patients.

Toxicity, GVHD, and Nonrelapse Mortality

Infections, mainly pneumonia, were diagnosed in 9 patients (21%). Six patients (14%) were treated for CMV reactivation, whereas 1 patient developed EBV reactivation after DLI. There was no significant difference in the incidence of CMV reactivations between sibling and MUD recipients (13% versus 22%, respectively, $P = .60$). Other complications occurred in 4 patients and are listed in Table 2.

Twenty-six patients (60%) developed aGVHD, which was grade II in 17 patients and grade III in 5 patients (Table 2). Two cases of grade III GVHD developed after DLI, and all patients with grade III GVHD died. The cumulative incidence of cGVHD was 33% at 1 and at 2 years. The incidence and severity of both aGVHD and cGVHD was similar in patients with related and unrelated donors ($P = .84$ and .74, respectively).

Four of patients died because of GVHD. No other TRM occurred and TRM was therefore 9%. In 4 other patients the cause of death was not transplantation-related (1 patient died after a complicated operation for Crohn's disease, the second patient expired because of a progressive dementia syndrome 3 years after HSCT, 1 patient experienced a sudden death while in CR without GVHD 1 year post-HSCT, and the fourth patient also died unexpectedly while being abroad 1.5 years after HSCT). Total nonrelapse mortality (NRM) was 19% (8 patients), with a cumulative

Table 2. *Complications*

Complications	
aGVHD	
Grade 0	15 (34%)
Grade 1	6 (14%)
Grade 2	17 (40%)
Grade 3	5 (12%)
Grade 4	0 (0%)
cGVHD	
Limited disease	8 (19%)
Extensive disease	6 (14%)
No	26 (60%)
Not applicable*	3 (7%)
CMV reactivation	
Yes	6 (14%)
No	37 (86%)
EBV reactivation	
Yes	1 (2%)†
No	42 (98%)
Other complications	
Infections	
No. of patients	9 (21%)
No. of episodes	15
Bronchiolitis obliterans	1 (2%)
Pulmonary embolism	1 (2%)
BMT nephropathy	1 (2%)
Intestinal perforation eci	1 (2%)

*Patients surviving < 100 days.
†After DLI.

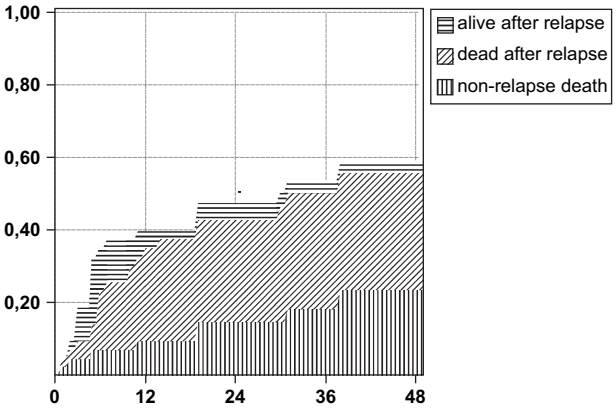

Figure 1. Cumulative incidence of relapse and non-relapse mortality (months).

incidence of NRM of 9% at 1 year, 15% at 2 years and 19% at 3 years (Figure 1).

Relapse and Survival

After a median follow-up of 19 months (range 1 to 58 months) 22 patients were alive, 20 in CR, and 2 in relapse. Median follow-up for survivors was 33 months (range: 14-58 months). Sixteen patients (37%) experienced relapse with a median DFS of 4 months (range: 1-24 months; see Table 3). The cumulative incidence of relapse was 30% at 1 year and 37% at 2 and at 3 years (Figure 1). In line with previous observations by our group [18], patients who did not develop complete donor chimerism or mixed chimerism with decreasing recipient signals between 1 and 3 months posttransplantation were at increased risk of relapse ($P = .01$).

One-year OS was 67%. Median DFS was 24 months, whereas median OS was 31 months (Figure 2). Fourteen DLIs were administered to 9 patients with (pending) relapse. Two of these patients are still alive, both 4 months after DLI.

Table 3. *Outcome*

Outcome	
Relapse	
Yes	**16 (37%)**
No	**27 (63%)**
Disease-free survival, months	
Median	**>24**
Range	**1-58**
DLI (No.)	
0	**34 (79%)**
1	**5 (12%)**
2	**3 (7%)**
3	**1 (2%)**
Death	
Yes	**21 (49%)**
No	**22 (51%)**
Overall survival, months	
Median	**31**
Range	**1-58**

Table 4 shows the univariate analysis of factors influencing outcome. Disease status was not included as a risk factor because only 5% of patients were not in CR at the time of transplantation. In univariate analysis AML risk was identified as a borderline significant prognostic factors for DFS not for OS. Poor-risk AML was also significantly associated with DFS in the multivariate analysis ($P = .02$).

DISCUSSION

Our analysis of 43 AML patients above the age of 40 years demonstrates that RIC HSCT might result in long-term DFS and OS in about half of the patients. These findings are underlined by the fact that the majority (67%) of the patients had a high leukemic risk

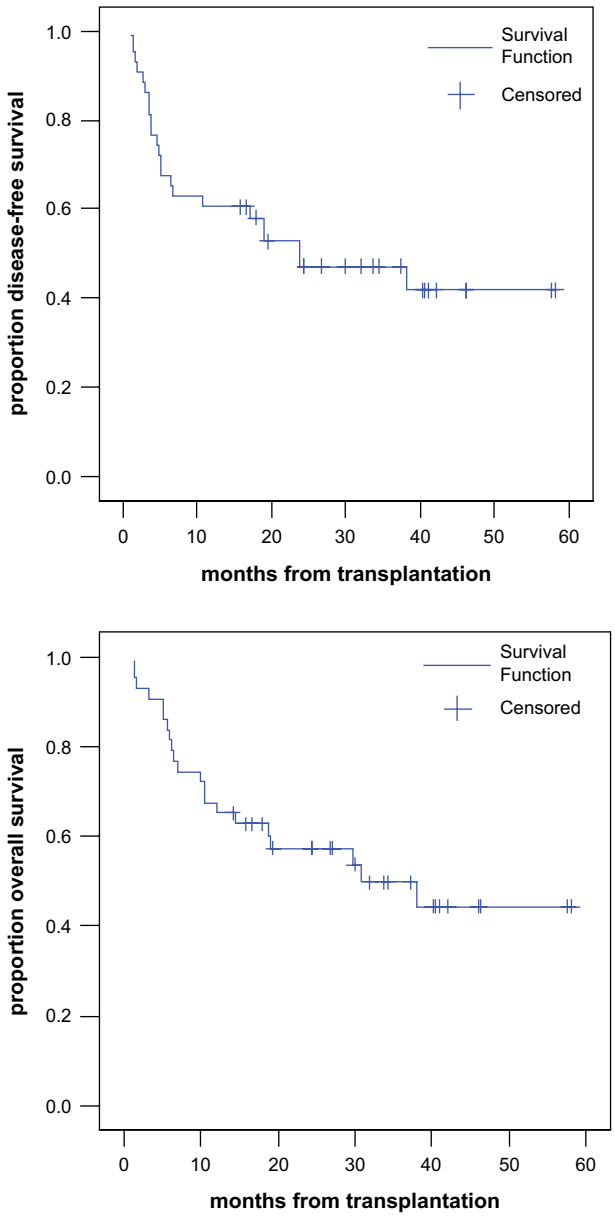

Figure 2. Probability of disease-free and overall survival.

Table 4. *Univariate Analysis of Prognostic Indicators of Disease-Free Survival (DFS) and Overall Survival (OS)*

	DFS			OS		
	OR	95% CI	P	OR	95% CI	P
Age						
≤ 60 years, n = 25	1.0			1.0		
> 60 years, n = 18	0.75	0.21-.266	0.66	2.36	0.68-8.15	0.18
Sex						
Male, n = 24	1.0			1.0		
Female, n = 19	2.2	0.62-7.70	0.22	0.90	0.27-3.00	0.86
Donor type						
Sibling, n = 28	1.0			1.0		
MUD, n = 15	2.86	0.76-10.53	0.12	2.00	0.56-7.16	0.29
AML risk						
Standard, n = 14	1.0			1.0		
High, n = 29	5.60	1.06-29.59	0.04	1.43	0.40-5.16	0.59
Timing of SCT						
Upfront, n = 32	1.0			1.0		
After relapse, n = 11	2.64	0.65-10.73	0.18	0.83	0.21-3.29	0.80
aGVHD						
Grade 0-1, n = 22	1.0			1.0		
Grade 2-4, n = 21	1.01	0.31-3.71	0.91	0.96	0.40-4.38	0.88

OR indicates odds ratio; CI , confidence interval; AML, acute myelogenous leukemia; MUD, matched unrelated donor; int, intermediate; SCT, stem cell transplantation; aGVHD, acute graft-versus-host disease.

profile. The patient group was selected on the basis of age limits. It has been shown that AML patients over the age of 40 years do not benefit from myeloablative HSCT because of increased TRM [19]. Interestingly, we did not find different outcomes for patients above or below the age of 60 years, which suggests that RIC HSCT is equally effective in all elderly AML patients above the age of 40 years. Furthermore, similar outcome for recipients of sibling or MUD grafts was demonstrated in our study.

Nearly all patients in our study were in CR before undergoing transplantation. Active disease at the time of RIC HSCT is associated with a high risk of relapse and poor outcome [11,20-22]. If the burden of leukemic cells is too high, the GVL effect is probably not strong enough or develops too late to overcome residual disease. Therefore, CR at the time of HSCT is a prerequisite for patient selection. As has been suggested by others [4], for those patients who are in CR, survival may be similar after RIC and myeloablative conditioning. However, no randomized trials are available to confirm this.

GVHD remains the major cause of NRM. Some studies have shown that in AML patients the incidence of GVHD is lower after RIC than following myeloablative conditioning [8,9], whereas others did not find different results [20]. In our analysis, none of the patients experienced grade IV aGVHD, but the incidence of grade II-III GVHD (52%) might be higher than in most previous reports (19%-42%) [2,11,21-25]. Nevertheless, the TRM was remarkably low in this elderly patient group (9%), and there were no differences between sibling and MUD transplants. This is probably related to the addition of ATG in the pretransplantation regimen for recipients of MUD grafts [26].

Our data on relapse and survival are rather preliminary because of the relatively short follow-up and small patient group. However, the 1-year DFS (61%) and OS (67%) rates are encouraging. Most previous RIC HSCT studies performed specifically in AML report a 2- or 3-year DFS ranging from 27% to 60% and an OS rate of 28% to 58% [9,11,21-25,27]. This wide range probably reflects heterogeneous patient selection and treatment protocols. Another important finding of our analysis is the comparable outcome in recipients of sibling and unrelated transplants, as has been observed by others [20,21,24]. Patients without a sibling donor are therefore suitable candidates for matched-unrelated transplants.

In conclusion, our report demonstrates that fludarabine plus low-dose TBI-based RIC HSCT is effective in AML patients over the age of 40 years without active disease at the time of transplant and is associated with low TRM.

REFERENCES

1. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med*. 1994;331:896-903.
2. Martino R, Caballero MD, Simon JA, et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. *Blood*. 2002;100:2243-2245.
3. Kolb HJ, Schmid C, Barrett AJ, Schendel DJ. Graft-versus-leukemia reactions in allogeneic chimeras. *Blood*. 2004;103: 767-776.

4. Baron F, Storb R. Hematopoietic cell transplantation after reduced-intensity conditioning for older adults with acute myeloid leukemia in complete remission. *Curr Opin Hematol*. 2007; 14:145-151.
5. Blaise D, Vey N, Faucher C, Mohty M. Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica*. 2007;92: 533-541.
6. Lazarus HM, Rowe JM. Reduced-intensity conditioning for acute myeloid leukemia: is this strategy correct. *Leukemia*. 2006;20:1673-1682.
7. Niederwieser D, Lange T, Cross M, Basara N, Al Ali H. Reduced intensity conditioning (RIC) haematopoietic cell transplants in elderly patients with AML. *Best Pract Res Clin Haematol*. 2006;19:825-838.
8. 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;19:2304-2312.
9. de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. *Blood*. 2004;104: 865-872.
10. Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. *Leukemia*. 2006;20:128-135.
11. Shimoni A, Hardan I, Shem-Tov N, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia*. 2006;20:322-328.
12. Mohty M, de Lavallade H, Ladaique P, et al. The role of reduced intensity conditioning allogeneic stem cell transplantation in patients with acute myeloid leukemia: a donor vs no donor comparison. *Leukemia*. 2005;19:916-920.
13. Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood*. 2007;109:1395-1400.
14. Finke J, Nagler A. Viewpoint: what is the role of allogeneic haematopoietic cell transplantation in the era of reduced-intensity conditioning—is there still an upper age limit? A focus on myeloid neoplasia. *Leukemia*. 2007;21:1357-1362.
15. 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.
16. Storb R, Yu C, Barnett T, et al. Stable mixed hematopoietic chimerism in dog leukocyte antigen-identical littermate dogs given lymph node irradiation before and pharmacologic immunosuppression after marrow transplantation. *Blood*. 1999;94: 1131-1136.
17. Thomas ED, Storb R, Clift RA, et al. Bone-marrow transplantation (second of two parts). *N Engl J Med*. 1975;292:895-902.
18. Huisman C, de Weger RA, de Vries L, Tilanus MG, Verdonck LF. Chimerism analysis within 6 months of allogeneic stem cell transplantation predicts relapse in acute myeloid leukemia. *Bone Marrow Transplant*. 2007;39:285-291.
19. Cornelissen JJ, van Putten WL, Verdonck LF, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? *Blood*. 2007;109:3658-3666.
20. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood*. 2005;105:1810-1814.
21. Hegenbart U, Niederwieser D, Sandmaier BM, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol*. 2006;24: 444-453.
22. Sayer HG, Kroger M, Beyer J, et al. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia: disease status by marrow blasts is the strongest prognostic factor. *Bone Marrow Transplant*. 2003;31:1089-1095.
23. Hallemeier C, Girgis M, Blum W, et al. Outcomes of adults with acute myelogenous leukemia in remission given 550 cGy of single-exposure total body irradiation, cyclophosphamide, and unrelated donor bone marrow transplants. *Biol Blood Marrow Transplant*. 2004;10:310-319.
24. Tauro S, Craddock C, Peggs K, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. *J Clin Oncol*. 2005;23: 9387-9393.
25. Wong R, Giralt SA, Martin T, et al. Reduced-intensity conditioning for unrelated donor hematopoietic stem cell transplantation as treatment for myeloid malignancies in patients older than 55 years. *Blood*. 2003;102:3052-3059.
26. Meijer E, Cornelissen JJ, Lowenberg B, Verdonck LF. Antithymocyteglobulin as prophylaxis of graft failure and graft-versus-host disease in recipients of partially T-cell-depleted grafts from matched unrelated donors: a dose-finding study. *Exp Hematol*. 2003;31:1026-1030.
27. Ho AY, Pagliuca A, Kenyon M, et al. Reduced-intensity allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning. *Blood*. 2004;104:1616-1623.