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Comparison of Reduced-Intensity Hematopoietic Cell Transplantation with Chemotherapy in Patients Aged 60–70 Years with Acute Myeloid Leukemia in First Remission

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Abstract

We compared the outcomes of acute myeloid leukemia (AML) patients aged 60–70 years receiving reduced-intensity allogeneic hematopoietic cell transplantation (HCT) in first remission (CR1) reported to the Center for International Blood and Marrow Research (CIBMTR) (N=94) with outcomes in patients treated with induction and post-remission chemotherapy on Cancer and Leukemia Group B (CALGB) protocols (N=96). All patients included had remained in CR1 for at least 4 months. HCT recipients were slightly younger than chemotherapy patients (median ages: 63 *v* 65 years; $P<0.001$), with no significant differences in the proportion with therapy-related leukemia or in different cytogenetic risk groups. Time from diagnosis to CR1 was longer for HCT recipients (median: 44 *v* 38 days; $P=0.031$). Allogeneic HCT was associated with significantly lower risk of relapse (32% *v* 81% at 3 years; $P<0.001$), higher non-relapse mortality (36% *v* 4% at 3 years; $P<0.001$), and longer leukemia-free survival (32% *v* 15% at 3 years; $P=0.001$). Although overall survival was longer for HCT recipients, this was not statistically significant (37% *v* 25% at 3 years; $P=0.08$). RIC allogeneic HCT in CR1 AML patients aged 60–70 years reduces relapse and improves leukemia-free survival. Strategies that reduce non-relapse mortality may yield significant improvements in overall survival.

Keywords

acute myeloid leukemia; allogeneic; reduced-intensity transplantation

INTRODUCTION

The outcome of acute myeloid leukemia (AML) patients aged 60 years or older treated with conventional cytotoxic chemotherapy remains poor, with few long-term survivors, irrespective of the induction chemotherapy or post-remission treatment intensity or duration (1–5). Immunological therapy in the form of allogeneic hematopoietic cell transplantation (HCT) performed in first complete remission (CR1) may offer a potential advantage in terms of leukemia-free survival (LFS) and overall survival (OS) in patients with adverse prognostic features (6–9), and those of intermediate-risk (10), due at least in part, to a graft-versus-leukemia (GvL) effect. Although the non-relapse mortality following allogeneic HCT using myeloablative regimens is approximately 20%, reported studies have rarely included patients older than 60 years. For older AML patients in CR1, the toxicity associated with myeloablative conditioning generally precludes its use with allogeneic HCT. Reduced-intensity conditioning (RIC) regimens with allogeneic HCT, however, have been better tolerated in older patients with acceptable non-relapse mortality (11–13). Compared to myeloablative regimens, allogeneic HCT following RIC regimens is associated with a reduction in non-relapse mortality (14). A recent Center for International Blood and Marrow Research (CIBMTR) study of RIC regimens in more than 500 patients with AML in CR1 showed similar outcomes in those from age 40 up to age >70 years (15). Other reported results using this approach are also encouraging (12–14, 16, 17), and suggest that RIC allogeneic HCT in older AML patients may improve their long-term outcome.

It is possible, however, that older AML patients undergoing RIC allogeneic HCT may be highly selected for better performance status and expected tolerance of the transplant-associated toxicity as suggested by a prospective feasibility analysis (18). Therefore, it

remains uncertain if broad application of HCT in the older, high-risk population will substantially improve outcome. No prospective studies comparing RIC allogeneic HCT with conventional chemotherapy in CR1 are reported. We present a comparison of RIC allogeneic HCT in AML patients aged 60 to 70 years reported to the CIBMTR with contemporaneous AML patients treated with chemotherapy alone on Cancer and Leukemia Group B (CALGB) protocols.

MATERIALS AND METHODS

Inclusion Criteria

The study population included 94 AML patients who received RIC allogeneic HCT and were reported to the CIBMTR between January 1999 and December 2005, and 96 AML patients who were treated with multidrug induction and post-remission chemotherapy after enrollment on CALGB protocols 9720 (19) and 10201(20) between January 1998 and October 2006. Patients were eligible for inclusion if they were aged 60–70 years, had *de novo* or treatment-associated AML, or AML evolving from a prior myelodysplastic or myeloproliferative disorder and had achieved CR1, and had not received an allogeneic HCT at any point in their subsequent disease course. Patients with AML-M3 were excluded. In addition, for CIBMTR cases, patients were included only if they had a RIC preparative regimen prior to related or unrelated peripheral blood or bone marrow stem cell transplantation in CR1. Patients receiving umbilical cord blood grafts were excluded. To minimize time to transplant selection bias, the analysis was limited to chemotherapy and transplanted patients who remained in CR1 for at least 4 months. The preparative regimen was considered RIC if it included combinations of the following: total body irradiation (TBI) <500 cGy in a single dose or <800 cGy if fractionated; and/or non-myeloablative doses of chemotherapy (total dose of Busulfan ≤ 9 mg/kg or Melphalan ≤ 150 mg/m^2). For non-transplanted (CALGB) cases, patients received induction chemotherapy with daunorubicin and cytarabine (± etoposide) and post-remission chemotherapy according to protocol as previously reported (19). Cytogenetic analyses for CALGB cases were centrally reviewed, while those of CIBMTR cases were as reported by the treating institutions. Cases were classified according to cytogenetic risk categories recently proposed by a consensus panel (21), although no consideration was given to molecular leukemia phenotyping as this was unavailable for the majority of patients.

Definitions of Clinical Endpoints

For this study, CR1 was defined as achievement of a bone marrow with <5% blasts after one or more cycles of induction chemotherapy. For transplanted (CIBMTR) cases, marrow cellularity and recovery of blood counts were not considered in the definition of CR1, while for chemotherapy treated (CALGB) cases, recovery of blood counts were required for CR, as previously defined (21). Also, for CALGB patients, those who failed to achieve CR after 2 cycles of induction treatment were considered primary refractory regardless of whether or not they achieved CR with later salvage chemotherapy and were excluded from this analysis. Patients who underwent transplantation (CIBMTR) were included if they were in first CR regardless of the number of lines of treatment used to achieve remission, as the number of induction courses required to achieve CR1 was not consistently captured in this group. Relapse was defined by >5% blasts in a bone marrow aspirate or the development of extramedullary leukemia in patients with previously documented CR. For both chemotherapy and allogeneic HCT patients, survival times were measured from the date of CR1 until either relapse or death (LFS), or death censoring for patients alive at last follow-up (OS). After allogeneic HCT, engraftment was defined as an absolute neutrophil count (ANC) ≥ 500/μl for 3 consecutive days. Grades II-IV acute graft versus host disease (GvHD) was determined in all transplanted patients (22), and chronic GvHD in the subpopulation

who survived 90 days or longer (23). For all cases, non-relapse mortality was defined as death during continuous CR1.

Statistical Analysis

Characteristics of transplant and chemotherapy groups were compared using Fisher's exact test for categorical variables and the Wilcoxon two-sample test for continuous variables. The outcome data in this study are left truncated. At each time point, the risk set in the chemotherapy cohort consisted of all patients still under study, while the risk set in the transplant cohort consisted of those whose time to transplant was less than the time point and were still on study. Univariable probabilities of OS and LFS were calculated using a left-truncated version of the Kaplan-Meier estimator (24) with 95% confidence intervals (CI). Relapse and non-relapse mortality were calculated using left-truncated version of cumulative incidence curves to accommodate competing risks. Left-truncated Cox proportional hazards regression models were used to evaluate the relative risk of patients receiving chemotherapy versus those receiving HCT. The proportionality assumption was tested by adding a time-dependent covariate. The proportionality assumption held up for all outcome end-points. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

The demographic characteristics of transplanted patients (n=94) and non-transplanted patients (n=96) are shown in Table 1. Transplanted patients were slightly, but significantly, younger than patients who were treated only with chemotherapy (median ages 63 *v* 65 years; $P<0.001$). Seventy-four percent of transplanted patients were between 60–65 years of age compared with 58% of non-transplanted patients ($P=0.022$). There was no significant difference in sex distribution, proportion of therapy-related leukemia, white blood cell count at diagnosis, FAB subtype, or the proportions of patients with favorable, normal, intermediate-II or adverse-risk karyotypes, between the transplanted and non-transplanted patients. Time from diagnosis to achievement of CR1 was longer for transplanted patients compared with chemotherapy-treated patients (median 38 days *v* 44 days; $P=0.031$). The median follow-up from the date of CR1 was 44 months for transplanted patients, compared with 51 months for chemotherapy-treated patients.

For chemotherapy patients, 69% received consolidation therapy on protocol at a median of 55 (range, 1–98) days from achieving CR1. Of those receiving consolidation therapy, the performance status was ECOG 1 in 78%, ECOG 2 in 20%, and ECOG 3 in 2%. The proportion of patients in the transplant group who received consolidation treatment before allogeneic HCT is unknown as the details for post remission therapy was not consistently captured for this group.

For transplanted patients, donors were HLA-identical siblings in 47%, well-matched (at least HLA-A, -B, and -DRB1 by molecular typing) unrelated donors in 30% of cases, and partially matched or unknown in the remainder (Table 1). In 93% of transplants, the stem cell source was peripheral blood. Preparative regimens generally combined fludarabine with melphalan (n=23), busulfan (n=24), low-dose TBI 200 cGy (n=25), or cyclophosphamide (n=12). GvHD prophylaxis included cyclosporine or tacrolimus in combinations with methotrexate in 31 patients, and cyclosporine or tacrolimus in 60 patients.

Non-relapse mortality

The cumulative incidence of death in CR1 from causes other than relapsed AML was significantly lower in chemotherapy-treated patients (P<0.001; Figure 1). At 3 years, the cumulative incidence of non-relapse mortality was 4% (95% CI: 1%–9%) for chemotherapy-treated patients compared with 36% (95% CI: 26%–46%) for those who received HCT. The specific causes of non-relapse deaths for chemotherapy-treated patients were not available. However, the most common causes of non-relapse deaths in transplanted patients included infection (n=14; including 8 with acute or chronic GvHD); GvHD (n=7), pneumonitis/adult respiratory distress syndrome (ARDS) (n=5), hemorrhage or other regimen-related toxicity (n=15).

Cumulative Incidence of Relapse

As shown in Figure 2, the risk of relapse was significantly higher among patients treated with chemotherapy (P<0.001). The cumulative incidence of relapse (CIR) at 3 years for chemotherapy-treated patients was 81% (95% CI: 71%–87%) compared with 32% (95% CI: 22%–42%) for patients receiving HCT. While few patients had favorable karyotypic abnormalities, allogeneic HCT appeared to be associated with lower CIR across all cytogenetic subgroups (P<0.001 for overall test; Table 2). The relative risk (RR) of relapse following chemotherapy was significantly worse than that following HCT (RR 3.47 [95% CI: 2.26–5.34]; P<0.0001).

Leukemia-free Survival

Figure 3 shows a significantly shorter LFS for chemotherapy-treated patients compared to those receiving allogeneic HCT (P=0.001). The median LFS for HCT patients was 15.7 months compared with 8.5 months for chemotherapy-treated patients. The 3-year LFS was 32% (95% CI: 23%–42%) for HCT patients compared with 15% (95% CI: 9%–23%) for patients treated with chemotherapy (Figure 3). Importantly, patients in all karyotypic subgroups appeared to have improved LFS with HCT compared with chemotherapy (Table 2). The RR of death or relapse following chemotherapy was significantly higher than after HCT [RR 1.72 (95% CI: 1.23–2.41), P=0.0014].

Overall Survival

Overall survival was longer for HCT patients, although this did not reach statistical significance (P=0.08; Figure 4). The median OS was 20.1 months for HCT patients versus 15.7 months for chemotherapy patients, and the 3-year OS was 37% (95% CI: 27%–47%) compared with 25% (95% CI: 17%–34%) for chemotherapy-treated patients. Overall survival also appeared better after HCT across all karyotype subgroups (Table 2). The RR of death following chemotherapy compared to HCT was 1.35 (95% CI: 0.97–1.89, P=0.076).

Transplant-specific Outcomes

For the 94 patients who received allogeneic HCT in CR1, engraftment occurred in 94% (95% CI: 88%–98%) of patients by 28 days post-HCT. The cumulative incidence of grade II-IV acute GvHD at 1 year was 39% (95% CI: 30%–49%) and chronic GvHD at 3 years was 39% (95% CI: 30%–50%).

DISCUSSION

Our results indicate that RIC allogeneic HCT performed in CR1 for AML patients aged 60 to 70 years is associated with a significant reduction in relapse rate and superior LFS compared to patients treated with chemotherapy alone. These favorable results appeared to occur in all cytogenetic subgroups. Our observations suggest that a GvL effect may be

operative following RIC transplantation in older AML patients and that a sizeable fraction of older patients under the age of 70 years can benefit from the anti-leukemic effect of HCT.

No prospective trials comparing RIC allogeneic HCT and chemotherapy have been reported. Patient and physician biases and limited healthy sibling donor availability may confound development of such a trial (18). Indeed, randomization to include unrelated or umbilical cord blood donors requires a completed donor search; an involved process that will not be undertaken unless an allograft is being actively considered by both the patient and the treating physician. Several reports describe results of RIC allogeneic HCT in older AML patients and suggest that significantly better survival may follow transplantation in CR1 (12, 25–27). While demonstrating the feasibility of RIC transplantation in older AML patients and encouraging, the reported studies have generally included only small numbers of patients 60 years or older, and often included patients beyond CR1(12, 25–27). These older patients may be highly selected for their interest and fitness to undergo allografting. Indeed, in a recent analysis assessing the feasibility of allogeneic HCT in patients 50 years or older with AML (and high-risk myelodysplasia), only 14 of 259 patients were eventually transplanted in CR1(28), demonstrating the difficulty of identifying and promptly evaluating older patients who might be candidates for allogeneic HCT. In this report, we include comparisons with patients who met eligibility criteria for enrollment on CALGB trials, reflecting at least some similar selection criteria albeit at the time of diagnosis, some months before assessing fitness for HCT. Despite our attempt to include comparable patients in the two cohorts, however, it acknowledged that some important differences exist. For example, in the chemotherapy group, patients who received allogeneic HCT in their subsequent disease course either in CR for as salvage for relapsed were excluded from analysis. However, as the proportion of older AML patients who typically proceed to transplantation, particularly after initial relapse, is expected to be very low (28), we believe that the impact of excluding patients who were later transplanted from the chemotherapy only group is likely to be minimal. Also, in this analysis, allogeneic HCT patients defined as being in CR1 could have received multiple lines of therapy to achieve remission, while only patients who achieved CR1 after no more than two course of induction were included in the chemotherapy group. The difference in definition of CR1 for the two groups in this analysis, however, is likely to bias against the outcome of the allogeneic HCT cohort as patients who achieve CR1 after more than two courses of chemotherapy might be expected to have more resistant leukemia compared to those who achieve CR1 after only one or two courses of induction chemotherapy. Notwithstanding these differences, our observations demonstrating the superiority of RIC allogeneic HCT compared with chemotherapy in these older AML patients remain clear.

We compared allogeneic HCT with chemotherapy in a sizeable number of older AML patients. To minimize the effect of selection and lead-time bias, we restricted our comparison to chemotherapy treated-patients who remained in CR1 for at least 4 months, as those with very early relapse would not be considered for transplantation (29). In a donor versus no donor analysis of 95 AML patients in CR1 with sibling donors, others demonstrated a significantly better LFS and OS for patients with a donor, suggesting that RIC allogeneic HCT in CR1 is superior to chemotherapy alone (28). However, the latter study included a majority of patients younger than 60 years, and many also received high-dose cytarabine or autologous stem cell transplantation consolidation prior to allogeneic HCT, limiting comparisons with our study.

Despite higher non-relapse mortality, our current study showed that allogeneic HCT in CR1 led to a significant reduction in relapse and improvement in LFS. It should be noted, however, that our study does not exclude a potential improvement in OS given its limited statistical power of only 37% to demonstrate a statistically significant difference of 12% for

OS at 3 years. We estimate that a study would require 250 patients in each group to have 80% power to demonstrate this difference in 3-year OS. Nonetheless, our results suggest that strategies aimed at reducing non-relapse mortality associated with allogeneic HCT could yield further improvements. The incorporation of antithymocyte globulin (ATG) or other *in vivo* T-cell depleting antibodies may limit the morbidity of acute GvHD and may lessen non-relapse mortality (25), although this may increase the risk of relapse (30). More recently, promising results of GvHD prophylaxis using sirolimus plus tacrolimus have been reported (31, 32), and are currently being studied in the Blood and Marrow Transplant Clinical Trials Network.

Although HCT led to a significant reduction in relapse, which seemed apparent in all cytogenetic subgroups, relapse remains a significant cause of treatment failure following allogeneic HCT in older AML patients. Indeed, our observed relapse risk is similar to that reported by other investigators following reduced intensity allogeneic HCT (25, 28, 29). Several strategies to reduce relapse may improve the efficacy of RIC allogeneic HCT, including the investigation of novel preparative regimens such as incorporating clofarabine with alkylating agents as recently tested in the myeloablative setting with promising results (33), use of hypomethylating agents before or after allogeneic HCT (34, 35), and immune-based strategies such as pre-emptive donor lymphocyte infusions (36) or vaccination against leukemia-specific antigens (37).

We conclude that RIC allogeneic HCT in AML patients 60 to 70 years old is feasible and is associated with a significant reduction in relapse and improvement in long-term outcome. Earlier referral for transplantation along with strategies directed at limiting non-relapse mortality, including better GvHD prophylaxis and treatment, may improve these outcomes for an even greater proportion of older patients with AML.

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APPENDIX

We would also like to acknowledge the following members of this Writing Committee:

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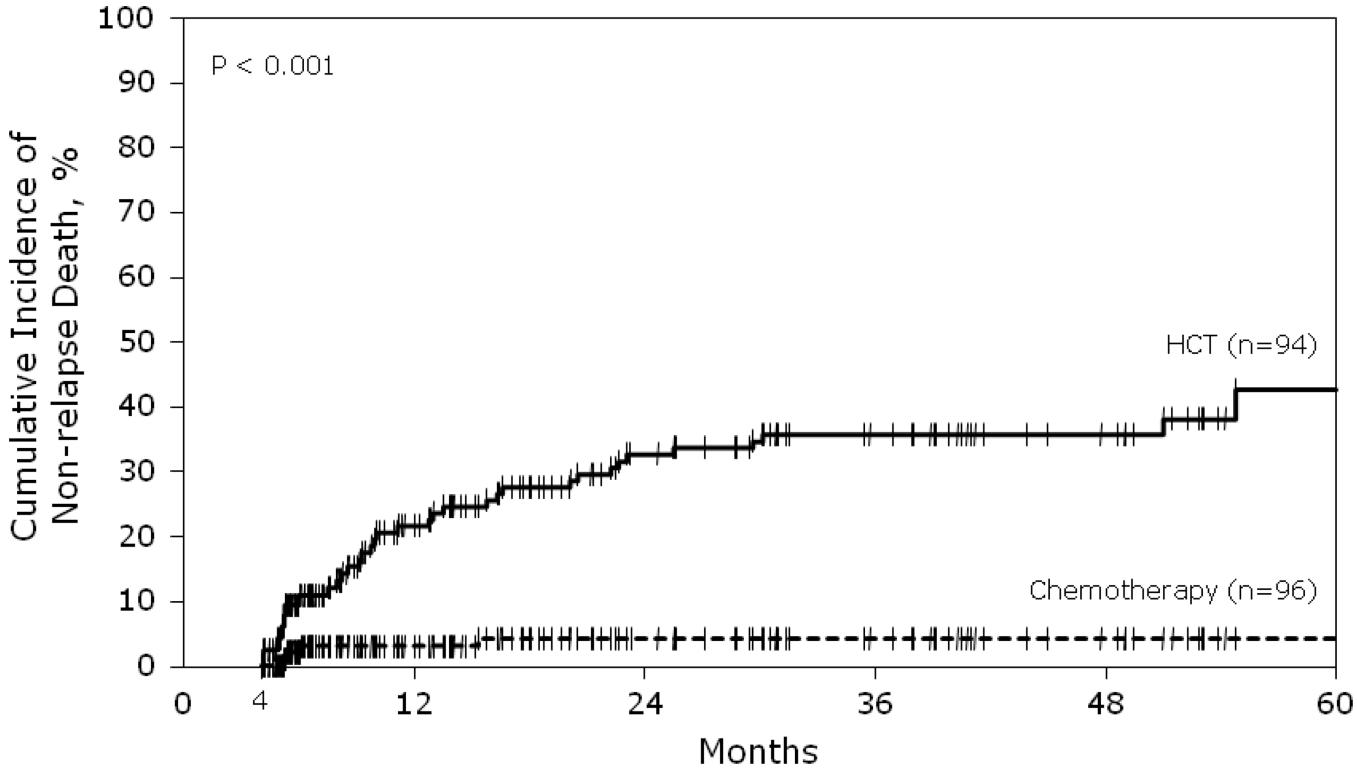

Figure 1.
Cumulative incidence of non-relapse death in CR1

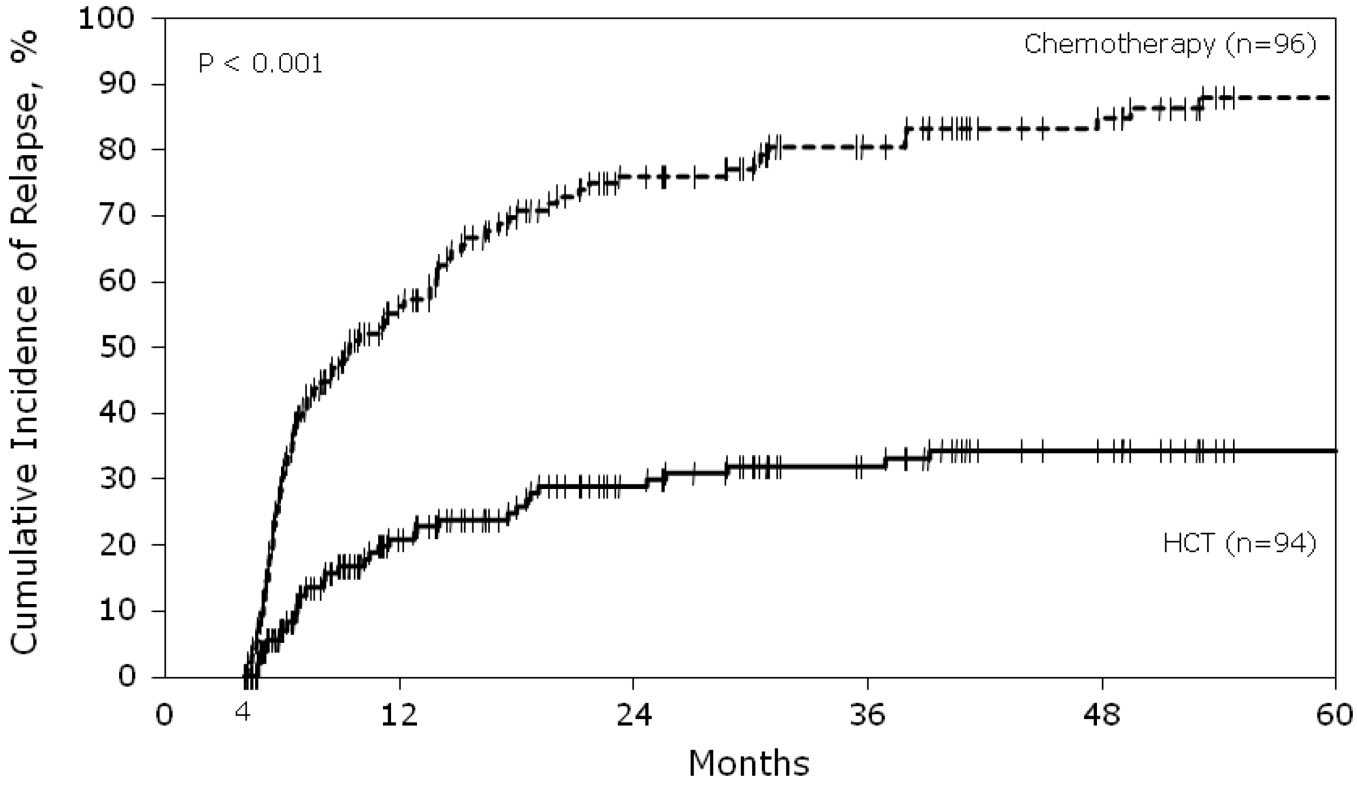

Figure 2.
Cumulative incidence of relapse.

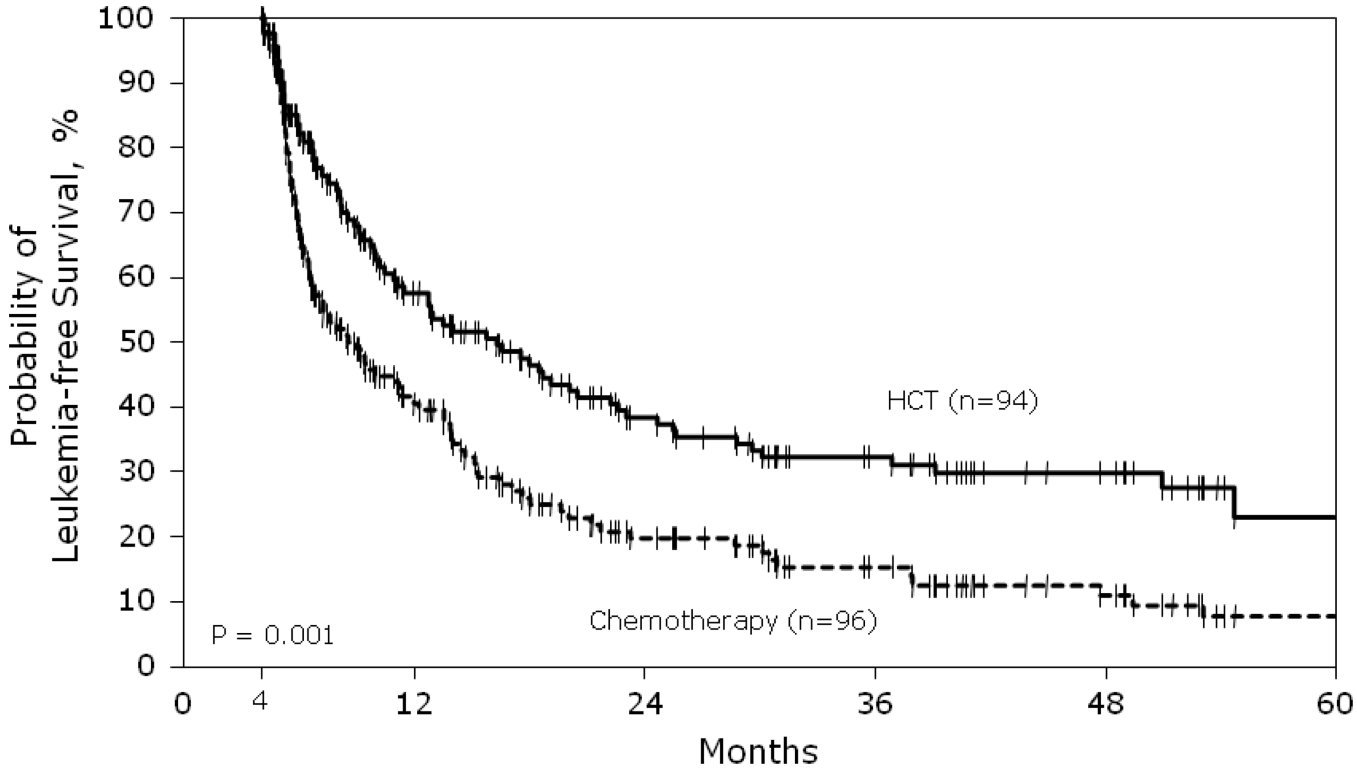

Figure 3.
Leukemia-free survival.

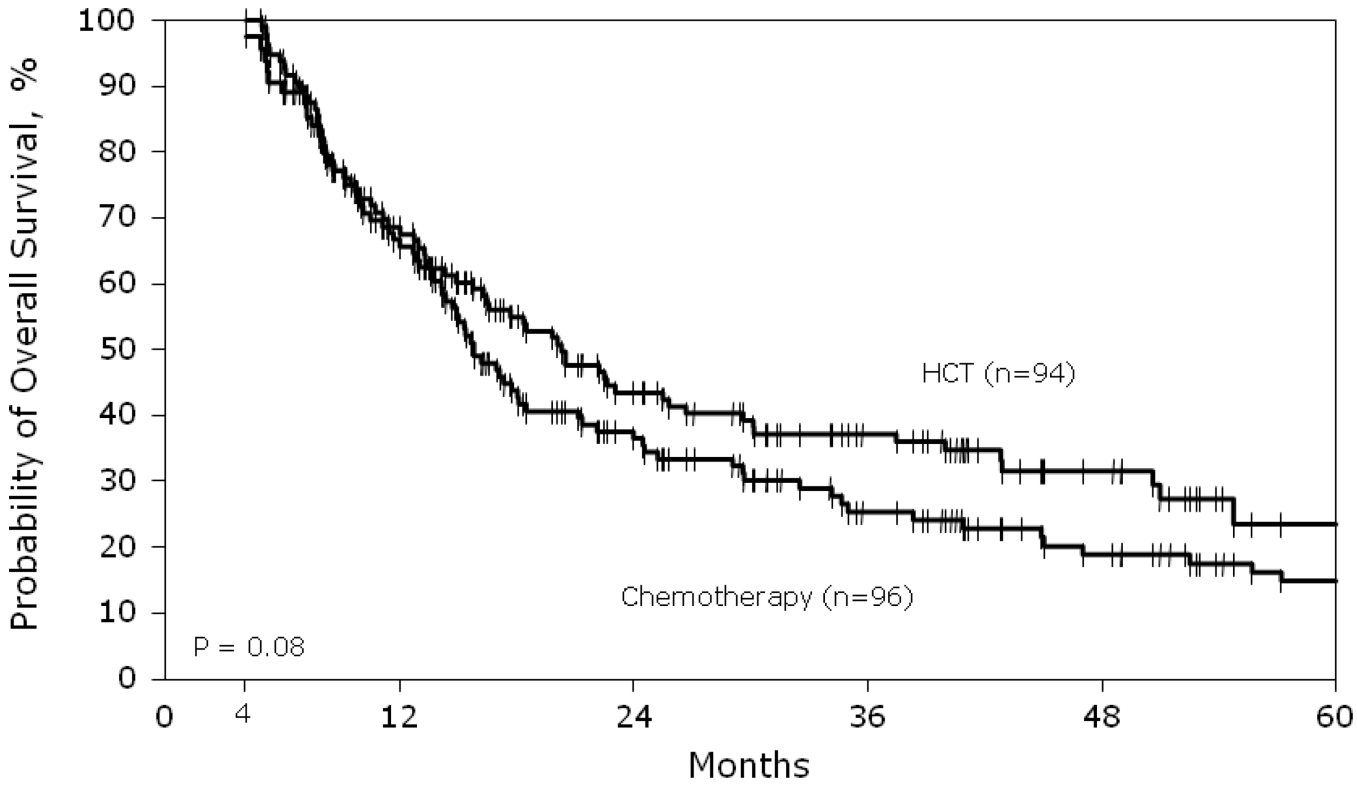

Figure 4.
Overall survival.

Table 1

Patient characteristics

	HCT (n=94)	Chemotherapy (n=96)	*P*-value
Age, median (range) in years	63 (60–70)	65 (60–70)	<0.001
Age distribution, n (%)			0.022
60–65 years	70 (74)	56 (58)	
66–70 years	24 (26)	40 (42)	
Male, n (%)	55 (59)	55 (57)	0.88
WBC at diagnosis (× 10^9/l), median (range) *	5.9 (0.5–216.0)	5.6 (0.8–191.7)	0.72
FAB classification, n (%) **			
M0	9 (10)	3 (6)	
M1	22 (23)	7 (13)	
M2	25 (27)	14 (26)	
M4	11 (12)	16 (30)	
M5	10 (11)	8 (15)	
M6	3 (3)	2 (4)	
M7	1 (1)	0 (0)	
Unclassified	13 (14)	4 (7)	
Therapy-related AML, n (%)	10 (11)	7 (7)	0.46
Cytogenetics, n (%) ***			0.32
Favorable	2 (2)	8 (8)	
Normal	44 (56)	52 (55)	
Intermediate-II	15 (19)	20 (21)	
Adverse	17 (22)	15 (16)	
Time from diagnosis to CR1 (days), median (range)	44 (10–251)	38 (24–211)	0.031
Transplant-related characteristics			
Time from diagnosis to transplant (days), median (range)	189 (63–828)	N/A	
Time from CR1 to transplant, n (%)		N/A	
<120 days	39 (41)		
120–180 days	28 (30)		
181–270 days	20 (21)		
>270 days	7 (7)		
Karnofsky score at transplantation ≥90% (n)	63	N/A	
Preparative regimen including, n (%)		N/A	
Melphalan ≤150 mg/m^2 (± other)	23 (24)		
Busulfan ≤ 9 mg/kg (± other)	24 (26)		
Fludarabine + TBI 200 cGy	23 (25)		
Fludarabine + cyclophosphamide	12 (13)		
TLI + ATG	5 (5)		
TBI 200 cGy	2 (2)		
TBI (<500 cGy single or <800 cGy fractionated dose)	3 (3)		

	HCT (n=94)	Chemotherapy (n=96)	*P*-value
Other	2 (2)		
GvHD prophylaxis, n (%)		N/A	
CsA or tacrolimus +MTX ± other	31 (33)		
CsA or tacrolimus ± other	60 (64)		
T-cell depletion	3 (3)		
Donor type, n (%)		N/A	
HLA-identical sibling	44 (47)		
Other related	5 (5)		
HLA-matched unrelated	28 (30)		
Partially matched unrelated	12 (13)		
Mismatched unrelated	2 (2)		
Unrelated (matching unknown)	3 (3)		
Graft type, n (%)		N/A	
Bone marrow	7 (7)		
Peripheral blood ± bone marrow	87 (93)		

Abbreviations: WBC, white blood cell count at presentation; FAB, French-American-British; CsA, cyclosporine A; MTX, methotrexate; N/A, not applicable, TBI, total body irradiation, TLI, total lymphoid irradiation, ATG, anti-thymocyte globulin, MTX, methotrexate.

*WBC at presentation is unknown for 10 HCT and 13 chemotherapy cases.

**FAB classification is unknown for 42 chemotherapy cases.

***Intermediate-II and Adverse cytogenetic categories as described in reference 21. Favorable comprises t(8;21)(p22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22).

Table 2

Estimated 3-year percentages of relapse, leukemia-free survival and overall survival by cytogenetic risk group*

	HCT	Chemotherapy	*P*-value
Cumulative Incidence of Relapse			<0.001
Favorable karyotype	0	69 (38–93)	
Normal	33 (20–47)	79 (68–88)	
Intermediate-II	25 (6–51)	90 (76–98)	
Adverse karyotype	45 (23–68)	80 (60–94)	
LFS			0.001
Favorable karyotype	100 (100–100)	19 (0–57)	
Normal	39 (24–55)	17 (8–28)	
Intermediate-II	30 (9–57)	10 (1–27)	
Adverse	22 (6–44)	13 (1–35)	
OS			0.08
Favorable karyotype	100 (100–100)	50 (18–82)	
Normal	45 (30–61)	27 (16–39)	
Intermediate-II	32 (10–59)	23 (7–45)	
Adverse	23 (7–45)	13 (1–35)	

Shown are the 3-year estimates (95% CI) for the endpoints shown. *P* value comparisons within these small cytogenetic subsets are not presented due to the small numbers. *P* values represent the overall adjusted comparisons between HCT and chemotherapy cohorts.

* Definitions of cytogenetic risk groups in the favorable and normal cytogenetic categories did not take into account molecular results.