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ORIGINAL ARTICLE

Significance of additional high-dose cytarabine in combination with cyclophosphamide plus total body irradiation regimen for allogeneic stem cell transplantation

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The combination of cyclophosphamide (CY) and total body irradiation (TBI) has been used as a standard conditioning regimen for allogeneic transplantation. Several studies showed an advantage of adding high-dose cytarabine (HDCA) to this regimen. To clarify the significance of additional HDCA, we conducted a retrospective multicenter study and compared the clinical results of these two regimens. From June 1985 to March 2003, 219 patients with hematological malignancies underwent allogeneic transplantation after conditioning with CY + TBI 12Gy ($n = 73$) or CA + CY + TBI 12Gy ($n = 146$). Engraftment, overall survival, transplant-related mortality (TRM), relapse rate and incidence of graft-versus-host disease (GVHD) were compared according to risks and donors. Addition of HDCA had no impact on the relapse rate in all subgroups, and it was associated with lower TRM among standard-risk patients after related transplantation, and with higher TRM and worse survival among standard-risk patients after unrelated transplantation. The incidence of acute GVHD was not significantly different between the two regimens, and HDCA resulted in a higher incidence of chronic GVHD among standard-risk patients after related transplantation. In summary, addition of HDCA is not beneficial for high-risk patients, and is not recommended for standard-risk patients receiving unrelated transplantation.

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Introduction

For allogeneic stem cell transplantation, the conditioning regimen is one of the most important factors. The combination of cyclophosphamide (CY) and total body irradiation (TBI) has been used as a standard conditioning regimen for myeloablative hematopoietic stem cell transplantation.[1–4] Intensification of the conditioning regimen using high-dose cytarabine (HDCA) has been investigated as possibly reducing disease relapse in hematological malignancies. Some studies are encouraging additional HDCA,[5–11] whereas others are reporting more toxicity using HDCA particularly on the heart and lung.[12–16] Our previous preliminary report did not show any significant differences between CY + TBI and CA + CY + TBI in a small cohort.[17]

To clarify the significance of additional HDCA, we conducted a retrospective multicenter study of 219 patients, and compared the clinical results of these two regimens. We confirmed that addition of HDCA neither did improve overall survival, nor reduce the relapse rate.

Patients and methods

Patients, conditioning regimen and GVHD prophylaxis
From June 1985 to March 2003, a total of 219 patients with various hematological malignancies from 13 institutes

underwent allogeneic stem cell transplantation after conditioning with either CY + TBI ($n = 73$) or CA + CY + TBI ($n = 146$). CY was given at a dose of 60 mg/kg once daily intravenously (i.v.) on days −5 and −4 (total dose 120 mg/kg), CA at a dose of 2 g/m^2 twice daily i.v. over 3 h on day −6 and 2 g/m^2 once daily i.v. over 3 h on days −5 and −4 (total dose 8 g/m^2) and TBI at a dose of 300 cGy fractions twice daily on days −2 and −1 (total dose 12 Gy). Seven institutions used only one regimen, either CY + TBI or CA + CY + TBI. The other six institutions used both regimens at the same time. There were no consistent indications for either regimen in any institution. Donors were HLA-fully-matched related donors or HLA-fully-matched unrelated donors. GVHD prophylaxis consisted of either cyclosporine (CsA) and short-term methotrexate (sMTX) or taclorimus (FK) and sMTX.

Statistical analysis

Engraftment, overall survival, transplant-related mortality (TRM), relapse rate and incidence of graft-versus-host disease (GVHD) were compared between the two regimens in each subgroup, which was defined according to risk (standard or high) and donor (related or unrelated). TRM was defined as mortality owing to any cause other than relapse or disease progression. Standard-risk patients are defined as those with acute myeloblastic leukemia (AML) or acute lymphoblastic leukemia (ALL) in first complete remission, chronic myelogenous leukemia (CML) in first chronic phase, or myelodysplastic syndromes (MDS) as refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS). High-risk patients were those with AML or ALL in subsequent complete remission, in relapse or of induction failure, Philadelphia-chromosome-positive ALL, CML in subsequent chronic phase, accelerated phase or blastic phase or MDS as RAEB or overt leukemia with MDS. The χ^2 test and Fisher's exact test were used for comparison of the two groups. Overall survival was calculated using the Kaplan–Meier method and *P*-values were calculated using the log-rank test. Cumulative incidence curves for TRM and relapse, with or without death, were constructed, reflecting time to relapse and time to TRM as competing risks. *P*-values were calculated at the fixed point in time as reported by Klein *et al.*[18] Univariate and multivariate analyses were performed using the Cox proportional hazard regression model, and variables were selected using stepwise method. A two-sided *P*-value of less than 0.05 was considered significant. Data were analyzed as of March 2003.

Results

Patient characteristics

Patient characteristics of each subgroup are summarized in Table 1. One hundred and twenty-seven patients received transplantation from a related donor whereas 92 received from an unrelated donor. GVHD prophylaxis consisted of CsA + sMTX in 182 patients and FK + sMTX in 37 patients. FK was used in one patient after related transplantation in 1999, and in 36 patients after unrelated

Table 1 Patient characteristics

Risk	*Standard*				*High*			
Donor	*Related*		*Unrelated*		*Related*		*Unrelated*	
Conditioning	*CY + TBI(19)*	*CA + CY + TBI(71)*	*CY + TBI(24)*	*CA + CY + TBI(40)*	*CY + TBI(14)*	*CA + CY + TBI(23)*	*CY + TBI(16)*	*CA + CY + TBI(12)*
Median age (range)	29 (20–50)	33 (16–53)	33 (18–54)	31 (17–50)	39 (24–51)	9 (16–44)	27 (15–48)	31 (16–50)
Sex, F/M	6/13	25/46	8/16	15/25	3/11	8/15	3/13	6/6
Diagnosis								
AML	5	26	2	4	5	6	3	3
ALL	8	18	4	16	3	10	9	4
CML	4	26	15	19	4	5	1	5
MDS	2	1	3	1	2	2	3	0
P-value[a]	0.25		0.09		0.31		0.41	
GVHD prophylaxis								
CsA + sMTX	18	71	10	26	14	23	11	9
FK + sMTX	1	0	14	14	0	0	5	3
P-value	0.48		0.12		—		1.0	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; CA = cytarabine; CML = chronic myelogenous leukemia; CY = cyclophosphamide; CsA = cyclosporine; FK = taclorimus; MDS = myelodysplastic syndromes; sMTX = short-term methotrexate; TBI = total body irradiation.
[a]Myeloid malignancy vs lymphoid malignancy.

transplantation since 1996. All stem cell sources were from bone marrow except for three patients who received peripheral blood stem cell transplantation from a related donor. Diagnosis and GVHD prophylaxis did not differ significantly between conditioning regimens in each subgroup. The median follow-up period of survivors was 979 days (range 31–4704 days).

Engraftment

All evaluable patients achieved sustained engraftment (an absolute neutrophil count of $>0.5\times10^9$/l for three consecutive days) in both regimens.

Overall survival

Overall survival did not differ significantly in any patient between the two regimens (58 vs 56% at 3 years, $P=0.90$) (Figure 1a). Addition of HDCA resulted in significantly worse survival among standard-risk patients after unrelated transplantation (45 vs 81% at 3 years, $P=0.02$) (Figure 1b), whereas it resulted in comparable survival among standard-risk patients after related transplantation (80 vs 60% at 3 years, $P=0.27$).

No significant differences were observed among high-risk patients (40 vs 40% at 3 years, $P=0.48$ among patients after related transplantation; and 11 vs 28% at 3 years, $P=0.93$ among patients after unrelated transplantation).

TRM and hazard analysis for TRM

TRM did not differ significantly in any patient between the two regimens (28 vs 32% at 3 years, $P=0.56$). Addition of HDCA was associated with significantly lower TRM among standard-risk patients after related transplantation (7.8 vs 35% at 3 years, $P=0.027$) (Figure 2a), whereas it resulted in higher TRM among standard-risk patients after unrelated transplantation (51 vs 19% at 3 years, $P=0.0082$) (Figure 2b).

No significant differences were observed among high-risk patients (22 vs 16% at 3 years, $P=0.65$ among patients after related transplantation; and 69 vs 58% at 3 years, $P=0.64$ among patients after unrelated transplantation).

Univariate analysis among standard-risk patients after related transplantation showed that addition of HDCA, female patients, age over 40 and GVHD prophylaxis with CsA + sMTX were significant factors affecting TRM. Addition of HDCA remained a significant factor on multivariate analysis (relative risk = 0.18; confidence interval, 0.052–0.63) (Table 2a). Univariate analysis among standard-risk patients, after unrelated transplantation, showed that addition of HDCA and GVHD prophylaxis

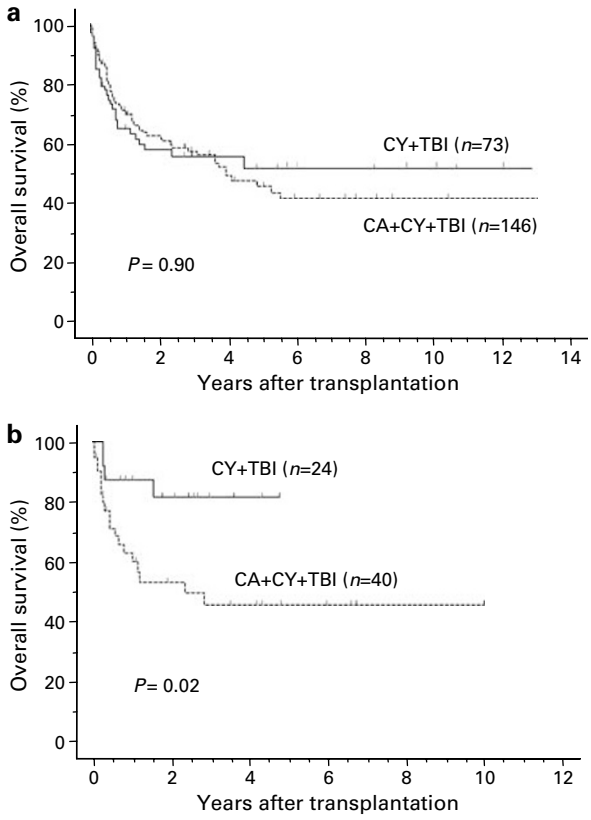

Figure 1 Overall survival. (**a**) No significant differences were observed between CA + CY + TBI and CY + TBI ($P=0.90$) in all patients. (**b**) CA + CY + TBI resulted in significantly worse survival than CY + TBI among patients who received transplantation from unrelated donors ($P=0.02$).

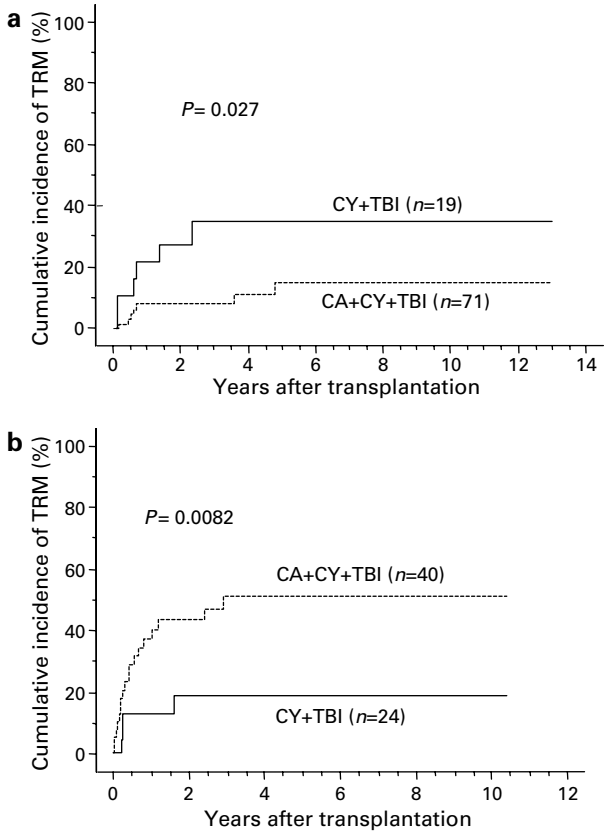

Figure 2 Cumulative incidence of TRM in patients with standard-risk disease. (**a**) CA + CY + TBI resulted in significantly lower TRM than CY + TBI among patients who received transplantation from related donors ($P=0.027$). (**b**) CA + CY + TBI resulted in significantly higher TRM than CY + TBI among patients who received transplantation from unrelated donors ($P=0.0082$).

Table 2 Prognostic factors affecting TRM

Variables	*Unfavorable factors*	*Univariate*		*Multivariate*[a]	
		Hazard ratio (CI)	P-*value*	*Hazard ratio (CI)*	P-*value*
(a) Related standard risk					
Conditioning	CA + CY	0.32 (0.11–0.94)	0.038	0.18 (0.052–0.63)	0.0070
Sex	Female	3.3 (1.1–10)	0.039	7.0 (2.0–25)	0.0030
Female to male	Yes	0.95 (0.29–3.1)	0.94		
Disease	Other than CML (CP)	1.4 (0.44–4.7)	0.55		
Age	>40	3.8 (1.2–12)	0.020	8.4 (2.4–30)	0.0010
GVHD prophylaxis	CsA + sMTX	0.12 (0.016–0.98)	0.047	0.53 (0.051–5.5)	0.59
Transplant year	~1996	1.9 (0.50–7.0)	0.35		
(b) Unrelated standard risk					
Conditioning	CA + CY	3.2 (1.1–9.3)	0.038	2.7 (0.90–8.1)	0.078
Sex	Female	0.70 (0.27–1.8)	0.45		
Female to male	Yes	0.74 (0.22–2.5)	0.63		
Disease	Other than CML (CP)	1.1 (0.46–2.5)	0.88		
Age	>40	1.1 (0.41–2.7)	0.93		
GVHD prophylaxis	CsA + sMTX	2.6 (1.0–6.6)	0.048	2.2 (0.84–5.6)	0.11
Transplant year	~1996	0.88 (0.29–2.6)	0.82		

Abbreviations: CA = cytarabine; CI = confidence interval; CML = chronic myelogenous leukemia; CsA = cyclosporine; CY = cyclophosphamide; sMTX = methotrexate.
[a]Final model.

of CsA + sMTX were significant factors influencing TRM. On multivariate analysis, addition of HDCA was associated with a trend for increased TRM (relative risk = 2.7; CI, 0.90–8.1) (Table 2b).

Relapse rate

Relapse rate did not differ between the two regimens (20 vs 13% at 3 years, $P = 0.23$). Addition of HDCA was not associated with any significant differences as to relapse rate in any subgroups (18 vs 5.6% at 3 years, $P = 0.085$ among standard-risk patients after related transplantation; 2.8 vs 0% at 3 years, $P = 0.31$ among standard-risk patients after unrelated transplantation; 51 vs 47% at 3 years, $P = 0.81$ among high-risk patients after related transplantation; and 17 vs 13% at 3 years, $P = 0.81$ among high-risk patients after unrelated transplantation).

Graft-versus-host disease

Results are summarized in Table 3. The incidence of grade II–IV acute GVHD did not differ between the two regimens in any subgroup. Addition of HDCA was associated with a significantly higher incidence of chronic limited and extensive GVHD among standard-risk patients after related transplantation (40/69 vs 5/19, $P = 0.029$).

Table 3 Incidence of acute and chronic GVHD

Risk	*Standard*		*High*	
Donor	*Related*	*Unrelated*	*Related*	*Unrelated*
Acute GVHD (II–IV)				
CY + TBI	6/19	6/24	3/11	8/14
CA + CY + TBI	9/71	11/40	6/22	6/11
P-value	0.11	1.0	1.0	0.78
Chronic GVHD				
CY + TBI	5/19	11/21	7/10	3/6
CA + CY + TBI	40/69	15/34	7/19	6/8
P-value	0.029	0.75	0.13	0.58

Abbreviations: CA = cytarabine; CY = cyclophosphamide; GVHD = graft-versus-host disease; TBI = total body irradiation.

Discussion

We examined a total of 219 patients, which is the largest series in the literature. Aurer and Gale[19] reviewed modified conditioning regimens in 1991, and failed to detect any major improvements in the overall survival with any of the new regimen. Although intensification of the conditioning regimen with HDCA is one of the approaches designed to improve outcome, particularly for high-risk hematological malignancies,[20–24] our retrospective analysis did not show any improvement in overall survival in any subgroups. In addition, no significant reduction in relapse rate was observed in any subgroups, suggesting that anti-leukemic activity may not be intensified by HDCA.

Many of the previous studies reported the superior anti-leukemic activity of HDCA for high-risk disease. Champlin *et al.*,[9] for example, showed that HDCA had good anti-leukemic activity before transplantation. Riddell *et al.*[21] reported a low relapse rate of 14% with the higher dose of CA (36 g/m^2), but an accurate relapse rate could not be fully evaluated because the day 100 TRM was as high as 50%. Mineishi *et al.*[22] reported a lower relapse rate of 11% after related transplantation compared to the 51% in our study. However, of 55 patients, 18 patients with AML/ALL with cytogenetic abnormalities in first remission were classified as high risk in their study. The difference in the definition of high-risk patients may be one reason for the lower relapse rate. In addition, the higher dose of CA (18 g/m^2) in their study may explain the lower relapse rate. Jillella *et al.*[10] also reported a similar outcome, but almost three-quarters of the patients had standard-risk disease. Woods

et al.[6] and Minami *et al*.[17] demonstrated a high relapse rate of 50–75% even with HDCA after related transplantation for high-risk disease. The dose effect of HDCA on anti-leukemic activity should be explored, but it may be offset by the increased toxicity reported in many earlier studies.

Interestingly, however, addition of HDCA was associated with lower TRM among standard-risk patients after related transplantation, and with higher TRM among standard-risk patients after unrelated transplantation. Thus, we performed multivariate analyses to clarify the factors affecting TRM, and confirmed that addition of HDCA still remained as a prognostic factor. Although the effects of the differences in unevaluable factors, such as supportive care, in each institute cannot be fully excluded, additional HDCA may play a role in the reduction of TRM after related transplantation. In contrast, a trend for increased TRM with HDCA after unrelated transplantation is reasonable. TRM is reported to be higher after unrelated than after related transplantation,[25,26] and intensification of the conditioning regimen increases TRM after unrelated transplantation.[27]

Intensity of conditioning is reported to modify the incidence of both acute and chronic GVHD,[28] but its effect on chronic GVHD is controversial.[29] Addition of HDCA was further associated with a significant increase in chronic GVHD among patients with standard-risk disease after related transplantation, but it was not associated with acute GVHD. Thus, other factors such as management of immunosuppresion may also have affected the incidence of chronic GVHD in our series.

In summary, addition of HDCA is not beneficial for patients with high-risk disease. It is not recommended for patients with standard-risk disease who will receive transplantation from unrelated donors because of increased TRM and decreased survival. It may be beneficial for patients with standard-risk disease who will receive transplantation from a related donor. Although the number of patients in this subgroup is somewhat small, such differences could not have emerged without underlying facts. Therefore, further studies are warranted to verify our results in this subgroup.

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