

## ORIGINAL ARTICLE

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

Y Inamoto<sup>1,14</sup>, T Nishida<sup>1,14</sup>, R Suzuki<sup>2</sup>, K Miyamura<sup>1</sup>, H Sao<sup>3</sup>, H Iida<sup>3</sup>, T Naoe<sup>4</sup>, F Maruyama<sup>5</sup>, N Hirabayashi<sup>6</sup>, M Hamaguchi<sup>7</sup>, T Iseki<sup>8</sup>, M Kami<sup>9</sup>, K Yano<sup>10</sup>, H Takeyama<sup>11</sup>, Y Morishita<sup>12</sup>, Y Morishima<sup>13</sup> and Y Kodera<sup>1</sup>

<sup>1</sup>Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan; <sup>2</sup>Division of Molecular Medicine, Aichi Cancer Center, Nagoya, Japan; <sup>3</sup>Department of Hematology, Meitetsu Hospital, Nagoya, Japan; <sup>4</sup>Department of Hematology, Nagoya University School of Medicine, Nagoya, Japan; <sup>5</sup>Department of Hematology, Fujita Health University School of Medicine, Toyoake, Japan; <sup>6</sup>Department of Hematology, Nagoya Daini Red Cross Hospital, Nagoya, Japan; <sup>7</sup>Department of Hematology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; <sup>8</sup>Department of Hematology and Oncology, Institute of Medical Science, University of Tokyo, Tokyo, Japan; <sup>9</sup>Department of Hematology, Toranomon Hospital, Tokyo, Japan; <sup>10</sup>Department of Hematology, Hamamatsu Medical Center, Shizuoka, Japan; <sup>11</sup>Department of Hematology, Ekisaikai Hospital, Nagoya, Japan; <sup>12</sup>Department of Hematology and Oncology, JA Aichi Showa Hospital, Konan, Japan and <sup>13</sup>Department of Hematology and Cell Therapy, Aichi Cancer Center, Nagoya, Japan

**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.**

*Bone Marrow Transplantation* (2007) **39**, 25–30.

doi:10.1038/sj.bmt.1705543; published online 20 November 2006

**Keywords:** cytarabine; cyclophosphamide; conditioning; allogeneic transplantation; anti-leukemic activity

## 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.<sup>1–4</sup> 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,<sup>5–11</sup> whereas others are reporting more toxicity using HDCA particularly on the heart and lung.<sup>12–16</sup> Our previous preliminary report did not show any significant differences between CY + TBI and CA + CY + TBI in a small cohort.<sup>17</sup>

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

Correspondence: Dr Y Inamoto, Department of HSCT Data Management, Nagoya University, School of Medicine, 1-1-20 Daiko Minami, Higashi-ku, Nagoya 461-0047, Japan.  
E-mail: yinamoto@js3.so-net.ne.jp

<sup>14</sup>These authors contributed equally to this study and should both be regarded as first authors.

Received 22 June 2006; revised and accepted 12 October 2006; published online 20 November 2006

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<sup>2</sup> twice daily i.v. over 3 h on day -6 and 2 g/m<sup>2</sup> once daily i.v. over 3 h on days -5 and -4 (total dose 8 g/m<sup>2</sup>) 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 tacrolimus (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  $\chi^2$  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.*<sup>18</sup> 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		
	Related		Unrelated		Related		Unrelated		P-value <sup>a</sup>
Donor	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)	
Conditioning	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 <sup>a</sup>		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 = cyclosporine; FK = tacrolimus; MDS = myelodysplastic syndromes; sMTX = short-term methotrexate; TBI = total body irradiation.  
<sup>a</sup>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  $>0.5 \times 10^9/l$  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

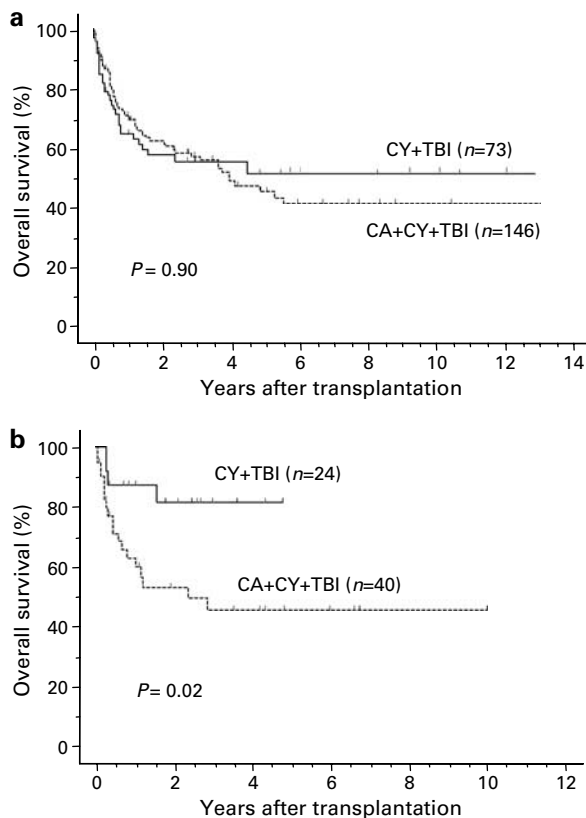
after related transplantation; and 11 vs 28% at 3 years,  $P=0.93$  among patients after unrelated transplantation).

### TRM and hazard analysis for TRM

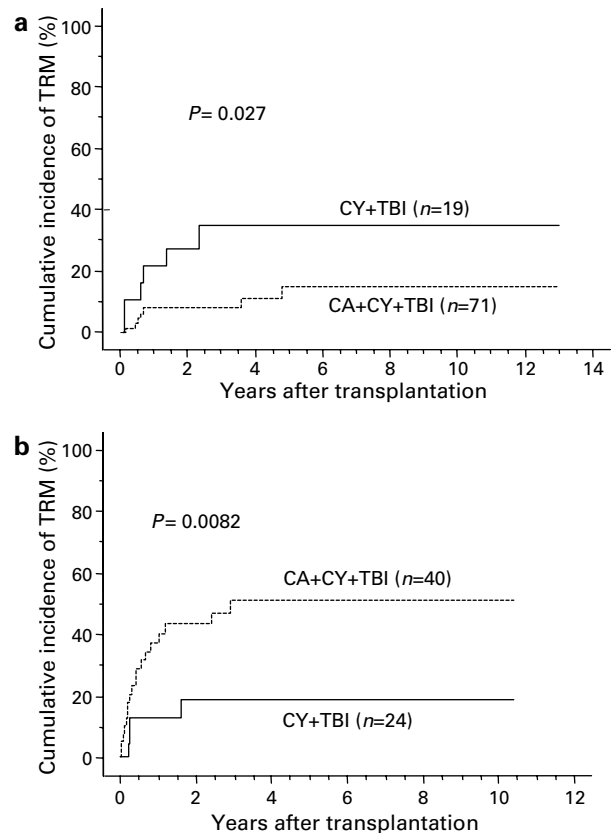
TRM did not differ significantly in any patient between the two regimens (28 vs 32% at 3 years,  $P=0.56$ ). Addition of HDCA was associated with significantly lower TRM among standard-risk patients after related transplantation (7.8 vs 35% at 3 years,  $P=0.027$ ) (Figure 2a), whereas it resulted in 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 <sup>a</sup>	
		Hazard ratio (CI)	P-value	Hazard ratio (CI)	P-value
<i>(a) Related standard risk</i>					
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		
<i>(b) Unrelated standard risk</i>					
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.

<sup>a</sup>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,  $P=0.029$ ).

#### Discussion

We examined a total of 219 patients, which is the largest series in the literature. Aurer and Gale<sup>19</sup> reviewed modified conditioning regimens in 1991, and failed to detect any major improvements in the overall survival with any of the new regimens. Although intensification of the conditioning regimen with HDCA is one of the approaches designed to improve outcome, particularly for high-risk hematological malignancies,<sup>20–24</sup> our retrospective analysis did not show

**Table 3** Incidence of acute and chronic GVHD

Risk	Standard		High	
	Related	Unrelated	Related	Unrelated
<i>Donor</i>				
<i>Acute GVHD (II–IV)</i>				
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
<i>Chronic GVHD</i>				
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.

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.*,<sup>9</sup> for example, showed that HDCA had good anti-leukemic activity before transplantation. Riddell *et al.*<sup>21</sup> reported a low relapse rate of 14% with the higher dose of CA (36 g/m<sup>2</sup>), but an accurate relapse rate could not be fully evaluated because the day 100 TRM was as high as 50%. Mineishi *et al.*<sup>22</sup> 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<sup>2</sup>) in their study may explain the lower relapse rate. Jillella *et al.*<sup>10</sup> also reported a similar outcome, but almost three-quarters of the patients had standard-risk disease. Woods

*et al.*<sup>6</sup> and Minami *et al.*<sup>17</sup> 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,<sup>25,26</sup> and intensification of the conditioning regimen increases TRM after unrelated transplantation.<sup>27</sup>

Intensity of conditioning is reported to modify the incidence of both acute and chronic GVHD,<sup>28</sup> but its effect on chronic GVHD is controversial.<sup>29</sup> 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 immunosuppression 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.

## Acknowledgements

We are indebted to the members of the Nagoya Blood and Marrow Transplantation Group for their helpful cooperation.

## References

- 1 Blaise D, Maraninchi D, Archimbaud E, Reiffers J, Devergie A, Jouet JP *et al.* Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytosine versus Cytosine-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood* 1992; **79**: 2578–2582.
- 2 Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD *et al.* Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood* 1990; **76**: 1867–1871.

- 3 Hansen JA, Gooley TA, Martin PJ, Appelbaum F, Chauncey TR, Clift RA *et al.* Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med* 1998; **338**: 962–968.
- 4 McGlave PB, Shu XO, Wen W, Anasetti C, Nademanee A, Champlin R *et al.* Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. *Blood* 2000; **95**: 2219–2225.
- 5 Weyman C, Graham-Pole J, Emerson S, August C, Champlin R, Coccia P *et al.* Use of cytosine arabinoside and total body irradiation as conditioning for allogeneic marrow transplantation in patients with acute lymphoblastic leukemia: a multi-center survey. *Bone Marrow Transplant* 1993; **11**: 43–50.
- 6 Woods WG, Ramsay NK, Weisdorf DJ, Haake R, Vallera DA, Kim TH *et al.* Bone marrow transplantation for acute lymphocytic leukemia utilizing total body irradiation followed by high doses of cytosine arabinoside: lack of superiority over cyclophosphamide-containing conditioning regimens. *Bone Marrow Transplant* 1990; **6**: 9–16.
- 7 Armitage JO, Gingrich RD, Klassen LW, Bierman PJ, Kumar PP, Weisenburger DD *et al.* Trial of high-dose cytarabine, cyclophosphamide, total-body irradiation, and autologous marrow transplantation for refractory lymphoma. *Cancer Treat Rep* 1986; **70**: 871–875.
- 8 Herzig RH, Coccia PF, Lazarus HM, Strandjord SE, Graham-Pole J, Cheung NK *et al.* Bone marrow transplantation for acute leukemia and lymphoma with high-dose cytosine arabinoside and total body irradiation. *Semin Oncol* 1985; **12**: 184–186.
- 9 Champlin R, Jacobs A, Gale RP, Ho W, Selch M, Lenarsky C *et al.* High-dose cytarabine in consolidation chemotherapy or with bone marrow transplantation for patients with acute leukemia: preliminary results. *Semin Oncol* 1985; **12**: 190–195.
- 10 Jillella AP, Doria R, Khan K, Zelterman D, Ahmad YH, Smith BR *et al.* Cyclophosphamide, cytosine arabinoside and TBI as a conditioning regimen for allogeneic bone marrow transplantation in patients with leukemia. *Bone Marrow Transplant* 1999; **23**: 1095–1100.
- 11 Nagatoshi Y, Okamura J, Ikuno Y, Akamatsu M, Tasaka H. Therapeutic trial of intensified conditioning regimen with high-dose cytosine arabinoside, cyclophosphamide and either total body irradiation or busulfan followed by allogeneic bone marrow transplantation for myelodysplastic syndrome in children. *Int J Hematol* 1997; **65**: 269–275.
- 12 Broun ER, Tricot G, Akard L, Nichols C, Cheerva A, Jansen J. Treatment of refractory lymphoma with high dose cytarabine, cyclophosphamide and either TBI or VP-16 followed by autologous bone marrow transplantation. *Bone Marrow Transplant* 1990; **5**: 341–344.
- 13 Petersen FB, Appelbaum FR, Buckner CD, Sanders JE, Clift RA, McGuffin R *et al.* Simultaneous infusion of high-dose cytosine arabinoside with cyclophosphamide followed by total body irradiation and marrow infusion for the treatment of patients with advanced hematological malignancy. *Bone Marrow Transplant* 1988; **3**: 619–624.
- 14 Trigg ME, Finlay JL, Bozdech M, Gilbert E. Fatal cardiac toxicity in bone marrow transplant patients receiving cytosine arabinoside, cyclophosphamide, and total body irradiation. *Cancer* 1987; **59**: 38–42.
- 15 Engelhard D, Elishoov H, Or R, Naparstek E, Nagler A, Strauss N *et al.* Cytosine arabinoside as a major risk factor for *Streptococcus viridans* septicemia following bone marrow transplantation: a 5-year prospective study. *Bone Marrow Transplant* 1995; **16**: 565–570.
- 16 Deconinck E, Cahn JY, Milpied N, Jouet JP, Vernant JP, Esperou H *et al.* Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia in first remission:

- long-term results for 42 patients conditioned with an intensified regimen (TBI, high-dose Ara-C and melphalan). *Bone Marrow Transplant* 1997; **20**: 731–735.
- 17 Minami S, Naito K. Comparison among three preconditioning regimens for allogeneic bone marrow transplantation in hematological malignancies. *Rinsho Ketsueki* 1990; **31**: 572–576.
  - 18 Klein JP, Rizzo JD, Zhang MJ, Keiding N. Statistical methods for the analysis and presentation of the results of bone marrow transplants. Part I: unadjusted analysis. *Bone Marrow Transplant* 2001; **28**: 909–915.
  - 19 Aurer I, Gale RP. Are new conditioning regimens for transplants in acute myelogenous leukemia better? *Bone Marrow Transplant* 1991; **7**: 255–261.
  - 20 Messner HA, Curtis JE, Minden MM. The combined use of cytosine arabinoside, cyclophosphamide, and total body irradiation as preparative regimen for bone marrow transplantation in patients with AML and CML. *Semin Oncol* 1985; **12**: 187–189.
  - 21 Riddell S, Appelbaum FR, Buckner CD, Stewart P, Clift R, Sanders J *et al*. High-dose cytarabine and total body irradiation with or without cyclophosphamide as a preparative regimen for marrow transplantation for acute leukemia. *J Clin Oncol* 1988; **6**: 576–582.
  - 22 Mineishi S, Longo WL, Atkinson ME, Smith EP, Hamielec M, Wiersma SR *et al*. Addition of high-dose Ara-C to the BMT conditioning regimen reduces leukemia relapse without an increase in toxicity. *Bone Marrow Transplant* 1999; **23**: 1217–1222.
  - 23 Bordigoni P, Esperou H, Souillet G, Pico J, Michel G, Lacour B *et al*. Total body irradiation-high-dose cytosine arabinoside and melphalan followed by allogeneic bone marrow transplantation from HLA-identical siblings in the treatment of children with acute lymphoblastic leukaemia after relapse while receiving chemotherapy: a Societe Francaise de Greffe de Moelle study. *Br J Haematol* 1998; **102**: 656–665.
  - 24 Sato N, Furukawa T, Kuroha T, Hashimoto S, Masuko M, Takahashi H *et al*. High-dose cytosine arabinoside and etoposide with total body irradiation as a preparatory regimen for allogeneic hematopoietic stem-cell transplantation in patients with acute lymphoblastic leukemia. *Bone Marrow Transplant* 2004; **34**: 299–303.
  - 25 Barker JN, Davies SM, DeFor TE, Burns LJ, McGlave PB, Miller JS *et al*. Determinants of survival after human leucocyte antigen-matched unrelated donor bone marrow transplantation in adults. *Br J Haematol* 2002; **118**: 101–107.
  - 26 Yanada M, Emi N, Naoe T, Sakamaki H, Takahashi S, Hirabayashi N *et al*. Tacrolimus instead of cyclosporine used for prophylaxis against graft-versus-host disease improves outcome after hematopoietic stem cell transplantation from unrelated donors, but not from HLA-identical sibling donors: a nationwide survey conducted in Japan. *Bone Marrow Transplant* 2004; **34**: 331–337.
  - 27 Kanda Y, Sakamaki H, Sao H, Okamoto S, Kodera Y, Tanosaki R *et al*. Effect of conditioning regimen on the outcome of bone marrow transplantation from an unrelated donor. *Biol Blood Marrow Transplant* 2005; **11**: 881–889.
  - 28 Perez-Simon JA, Diez-Campelo M, Martino R, Brunet S, Urbano A, Caballero MD *et al*. Influence of the intensity of the conditioning regimen on the characteristics of acute and chronic graft-versus-host disease after allogeneic transplantation. *Br J Haematol* 2005; **130**: 394–403.
  - 29 Couriel DR, Saliba RM, Giralt S, Khouri I, Andersson B, de Lima M *et al*. Acute and chronic graft-versus-host disease after ablative and nonmyeloablative conditioning for allogeneic hematopoietic transplantation. *Biol Blood Marrow Transplant* 2004; **10**: 178–185.