Allogeneic Marrow Transplantation in Patients With Acute Myeloid Leukemia in First Remission: A Randomized Trial of Two Irradiation Regimens

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A randomized trial of 12.0 Gy versus 15.75 Gy of total body irradiation (TBI) was performed in patients with acute myeloid leukemia undergoing allogeneic marrow transplantation while in first complete remission. All patients received 120 mg/kg cyclophosphamide followed by TBI and marrow from HLA-identical siblings. Cyclosporine and methotrexate were used for prophylaxis against acute graft-versus-host disease (GVHD). Thirty-four patients received 2.0-Gy fractions of irradiation daily for 6 days and 37 received 2.25-Gy fractions daily for 7 days. The 3-year actuarial probabilities for relapse-free survival were 0.58 for the patients who received 12.0 Gy and 0.59 for those who received 15.75 Gy. The 3-year probabilities of relapse were 0.35 for the 12.0 Gy group and 0.12 for the 15.75 Gy group ($P = .06$). The 3-year probabilities of transplant-related mortality were 0.12 and 0.32, respectively ($P = .04$). The probability of moderate to severe acute GVHD was 0.21 for the 12.0 Gy group and 0.48 for the 15.75 Gy group ($P = .02$). Patients exposed to the higher irradiation dose received less immunoprophylaxis against, and had a higher incidence of, acute GVHD. The increased dose of TBI significantly reduced the probability of relapse but did not improve survival because of increased mortality from causes other than relapse.

BETWEEN 1976 and 1978 the Seattle Marrow Transplant Team established the efficacy of allogeneic marrow transplantation as early consolidation therapy for patients with acute myeloid leukemia (AML) in first remission.[1] Nineteen patients received HLA-identical marrow transplants after preparation with 120 mg/kg cyclophosphamide (CY) and a single exposure of 9.2 Gy of total body irradiation (TBI). Methotrexate (MTX) was administered for 102 days posttransplant as prophylaxis against acute graft-versus-host disease (GVHD). Nine of these 19 patients are in unmaintained first remission 11 to 13 years posttransplantation.[2] These initial results of allogeneic transplantation for AML in first remission have been confirmed by many investigators.[3-7]

Since 1978 a series of randomized controlled trials has been conducted to evaluate approaches for improving the survival of patients transplanted during first remission of AML.[8-11] Trials in patients with advanced leukemia suggest that 15.75 Gy TBI administered in 2.25-Gy daily fractions is the maximum exposure that can be tolerated after 120 mg/kg CY followed by an allograft.[12-14] This report summarizes the results of a randomized trial comparing the effectiveness of 12.0 Gy with 15.75 Gy TBI in patients with AML in first remission receiving GVHD prophylaxis with cyclosporine (CSP) and MTX.

MATERIALS AND METHODS

Between April 26, 1985, and September 1, 1988, 72 consecutive patients with AML in first complete remission were registered in a protocol for allogeneic marrow transplantation from HLA-identical siblings. One patient was excluded from analysis for failure to meet remission criteria. Patients were referred for transplantation after a variety of induction regimens and with differing approaches to consolidation and maintenance treatment. All patients were randomized to receive either 12.0 Gy or 15.75 Gy of TBI before transplantation.

Patient eligibility. Patients were categorized as being in remission if the marrow was of normal cellularity and contained fewer than 5% blasts and the peripheral blood hemogram had a granulocyte count $>1.0 \times 10^9$/L and a platelet count $>100 \times 10^9$/L with an adequate transfusion-independent hematocrit. No patient had extramedullary disease at the time of transplant.

Preparative regimens. All patients received 60 mg/kg CY intravenously (IV) on each of 2 successive days followed by TBI delivered from opposing ^{60}Co sources at a rate of 6 to 7 cGy/min.[8] Thirty-four patients were randomized to receive TBI in 2.0-Gy daily fractions for 6 days, and 37 patients were randomized to receive TBI in 2.25-Gy fractions daily for 7 days. Marrow was infused within 24 hours of the last TBI exposure, and the day of infusion was designated day 0.

Posttransplant immunosuppression. All patients were scheduled to receive 15 mg/m^2 IV MTX on day 1 and 10 mg/m^2 on days 3, 6, and 11. All patients received CSP[10] in one of two concurrent randomizations. Sixty-six patients received CSP starting on the day before marrow infusion (day -1) in a dose of 3 mg/kg/d IV given in two divided doses. Five patients (two in the 12.0-Gy group and three in the 15.75-Gy group) received CSP at a dose of 1.5 mg/kg/d IV from days -1 through 15 postgrafting followed by resumption of full doses. Oral CSP, 12.5 mg/kg/d, was substituted for the IV route when tolerated. Doses of CSP were adjusted when necessary because of renal or hepatic dysfunction and MTX dosage was adjusted for mucositis or ascites. Ten patients (six in the 12.0-Gy group and four in the 15.75-Gy group) were randomized to have CSP discontinued on day 60 if they had no evidence of acute GVHD, whereas the

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remainder were scheduled to have a 5% weekly reduction in the dose of CSP beginning on day 100 with discontinuation on day 180. Fifteen patients (seven in the 12.0-Gy group and eight in the 15.75-Gy group) were randomized to receive early prednisone in addition to the CSP and MTX. Prednisone was administered at a dose of 1 mg/kg/d IV from days 0 to 21 and 0.5 mg/kg from days 22 to 35. Acute GVHD was treated with prednisone, antithymocyte globulin, or monoclonal antibodies.[15,16] Chronic GVHD was treated with prednisone alone or in combination with CSP.[17]

Tissue typing studies. Donors and recipients were HLA-identical siblings as determined by serologic typing for HLA-A, -B, -DR, and -DQ, and mixed leukocyte culture tests.[18]

Causes of death. Patients dying after posttransplant relapse were categorized as dying of leukemia irrespective of the proximate cause. Deaths in patients who had not relapsed were categorized as transplant-related mortality. Infection was listed as the cause of death when bacterial, viral, or fungal infection other than interstitial pneumonia was the proximate cause of death. Infections were further categorized as associated or not associated with GVHD.

Informed consent. Risks of the treatment protocols were fully explained to patients, donors, and relatives. Informed consent was obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Statistical analysis. The endpoints of analysis were duration of remission (from transplantation until relapse, censored by death or end of follow-up) and relapse-free survival (from transplantation until relapse or death, censored by the end of the follow-up). Patients were considered to be at risk for transplant-related mortality from the day of transplant until relapse or the end of follow-up. Distributions of remission duration and relapse-free survival were estimated by the method of Kaplan and Meier.[19] Events were recorded through April 1990. Durations of follow-up were calculated to the latest date of contact with each patient. Levels of statistical significance were calculated by the Mantel-Cox statistic.[20]

RESULTS

Patient characteristics. Table 1 presents the hematologic values at the time of diagnosis. Cytogenetic data at the time of diagnosis were available for only 13 patients in each group, too few for meaningful analysis.

Table 1. Hematologic Characteristics at Diagnosis

	Study Groups*	
	12.0 Gy (N = 34)	15.75 Gy (N = 37)
Peripheral blood		
WBC count including blasts ($\times 10^{-9}$/L)		
Patients with unknown values	1	5
Median (range)	15 (1-155)	8 (0.6-310)
<1	0	2
>100	3	4
Blast count ($\times 10^{-9}$/L)		
Patients with unknown values	6	6
Median (range)	3 (0-139)	2.6 (0-269)
>100	2	4
Platelet count ($\times 10^{-9}$/L)		
Patients with unknown values	1	7
Median (range)	51 (2-195)	40 (6-470)
<20	4	9
Marrow		
Blast count (%)		
Patients with unknown values	7	8
Median (range)	66 (8-95)	70 (12-100)

*Groups are designated by the TBI regimen.

Table 2. Pretransplant Characteristics

	Study Groups*		
	12.0 Gy (N = 34)	15.75 Gy (N = 37)	
Age (y)			
<18	3	7	
Median (range)	26 (6-53)	25 (3-47)	
Morphology			
FAB			
1 or 2	23	20	
3	1	6	
4	7	7	
5	1	2	$P = .42$
6	0	1	
7	1	1	
Biphenotypic	1	0	
Cytomegalovirus			
Donor and recipient both seronegative	2	8	
Recipient seropositive	20	20	$P = .15$
Days from remission to transplant:			
Median (range)	61 (10-189)	65 (13-293)	
Induction courses			
1	20	24	
2	11	6	
3	2	5	$P = .34$
4	1	2	
Consolidation courses			
0	24	27	
1	7	8	
2	1	2	$P = .48$
3	2	0	

Abbreviation: FAB, Franco-American-British classification.
*Groups are designated by the TBI.

Table 2 presents the patient characteristics at the time of transplant. Seven patients in the 12.0-Gy group and eight patients in the 15.75-Gy group received regimens containing high-dose cytarabine for initial induction or for consolidation.

Engraftment. Seventy patients had successful engraftment as documented by recovery of peripheral granulocyte and platelet counts. This was confirmed by cytogenetic markers when donor and recipient were of the opposite sex. One patient in the 12.0-Gy group died on day 42 without significant evidence of hematopoietic engraftment (maximum granulocyte count of 0.24×10^9/L and an aplastic marrow) but with acute GVHD of the skin.

Transplant-related deaths. The probabilities of transplant-related mortality are shown in Fig 1, and Table 3 summarizes the causes of death in both groups. The difference in transplant-related mortality was statistically significant ($P < .04$).

Acute GVHD. The actuarial probability of developing grade 2 or worse acute GVHD was significantly higher in the 15.75-Gy group than in patients who received 12.0 Gy ($P = .02$, Fig 2).

Thirty-four patients in the 12.0-Gy group and 35 patients

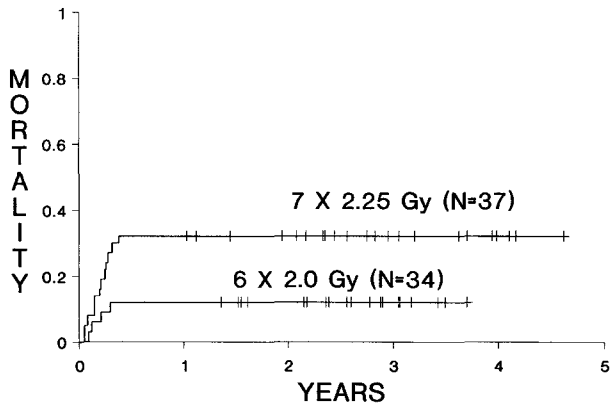

Fig 1. Mortality in patients not relapsing after marrow transplantation ($P = .04$). Patients who relapsed were censored at the time of relapse.

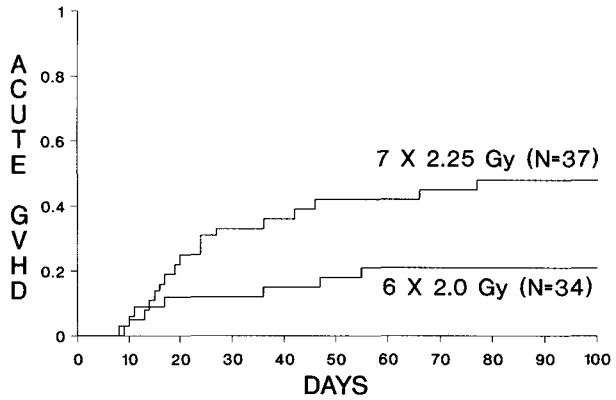

Fig 2. Probability of developing grade 2 through 4 acute graft-versus-host disease ($P = .02$).

in the 15.75-Gy group survived more than 28 days. Twenty-nine patients received 100% of the prescribed MTX and more than 80% of the prescribed CSP during the first 28 days posttransplant. Seventeen of these patients were in the 12.0-Gy group, and 12 were in the 15.75-Gy group. Only 1 of these patients developed grade 2 or worse acute GVHD, but clinical extensive chronic GVHD occurred in 8 (6 in the 12.0-Gy group and 2 in the 15.75-Gy group). Among these 29 patients there were six relapses and five deaths (all in relapsed patients) in the 12.0 Gy group and no relapses or deaths in the 12 patients who received 15.75 Gy. The actuarial probabilities of relapse in these 29 patients who received full doses of MTX and CSP were 0.37 at 2 years in the 12.0-Gy group and 0.00 in the 15.75-Gy group ($P = .03$).

Effects of prednisone administered for GVHD prophylaxis. Seven patients in the 12.0-Gy group received early prednisone, and there were no transplant-related deaths and one relapse in this group. In the 15.75-Gy group eight patients received early prednisone, and three died of transplant-related causes and none of relapse.

Table 3. Survival

	Study Groups*	
	12.0 Gy (N = 34)	15.75 Gy (N = 37)
Alive in continuous remission	20	22
Alive after relapse	2	0
Transplant deaths†	4	12
Causes of death		
Relapse	8	3
Acute GVHD		
With infection or hemorrhage	1	4
With CMV pneumonia	1	3
With EBV lymphoma	0	1
Chronic GVHD with infection	0	1
VOD of liver	1	3
Graft failure and infection	1	0
Total deaths	12	15

Abbreviations: VOD, venocclusive disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

*Groups are designated by the TBI regimen.

†Patients who died of causes other than relapse.

Relapse. The probability of relapse censored for other causes of death is shown in Fig 3 and was 0.35 in the 12.0-Gy group and 0.12 in the 15.75-Gy group ($P = .06$).

Survival. Twenty-two of 34 patients in the 12.0-Gy group survive, 20 of them disease free, between 498 and 1,350 days posttransplant. Twenty-two of 37 patients in the 15.75-Gy group survive, all disease free, between 375 and 1,681 days posttransplant. Figure 4 presents the actuarial probability of relapse-free survival for both groups of patients and Table 4 describes the current status of the survivors who have not relapsed after the transplant procedure.

DISCUSSION

An important observation in this randomized study was the high actuarial probability of relapse censoring for other causes of death (35%) following 12.0 Gy of TBI and posttransplant immunosuppression with CSP and MTX. With a regimen of 15.75 Gy TBI using the same combination of MTX and CSP, the relapse probability was only 13% ($P < .06$). This result represents one of the few demonstrations that increasing the dose of TBI can reduce the probability of relapse.

There was a significantly higher incidence of serious acute GVHD in the 15.75-Gy group. Patients in this group received less of the prescribed MTX and CSP than patients

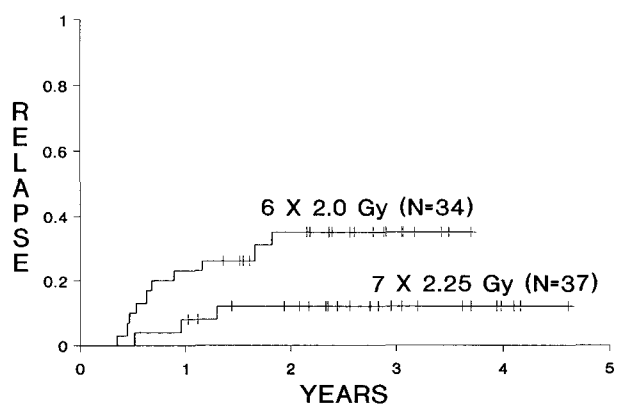

Fig 3. Probability of relapse ($P = .06$).

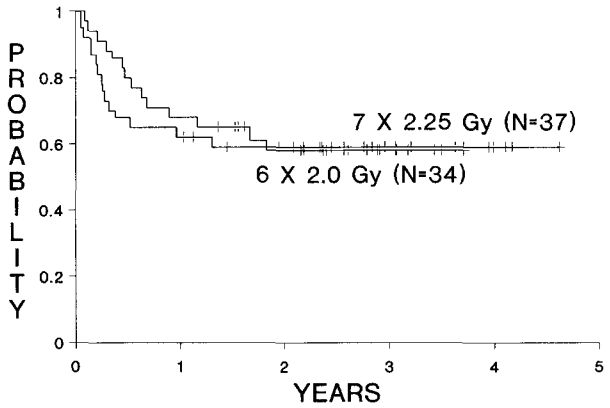

Fig 4. Probability of surviving relapse-free after transplantation.

in the 12.0-Gy group, presumably as a consequence of toxicity from the radiation schedule. It is not possible to assess whether the apparent increase in the risk of developing serious acute GVHD in the 15.75-Gy group resulted from this reduced prophylaxis. Increased tissue damage from the higher dose of TBI may have predisposed to GVHD or enhanced the clinical manifestations of acute GVHD.

It could be argued that the lower relapse rate in patients receiving 15.75 Gy was due to the increased incidence of acute GVHD in this group and not to the increased dose of TBI. Previous analyses from this institution have failed to demonstrate a direct effect of acute GVHD on relapse in patients with AML transplanted while in first complete remission.[21,22] In both groups acute GVHD was absent in patients who received most of the prescribed regimen of GVHD prophylaxis, and yet the different TBI regimens were associated with significantly different probabilities of relapse. This pattern suggests that the TBI regimens had differing direct antileukemic efficacy.

In this study the decrease in relapse rate following 15.75 Gy of TBI was offset by an increase in transplant-related deaths. The increased dose of TBI was associated with a substantial and significant increase in transplant-related deaths, but these were almost all associated with acute GVHD. There was neither transplant-related mortality nor acute GVHD in the patients who received GVHD prophylaxis as prescribed. Thus, the increased mortality associated with increased exposure to TBI was in part a consequence of increased acute GVHD in patients whose GVHD prophylaxis was obstructed by radiation-induced tissue damage.

Table 4. Current Status of Survivors

	Study Groups*	
	12.0 Gy (N = 34)	15.75 Gy (N = 37)
Alive and well No history of chronic GVHD Karnofsky score = 100%	10	15
Alive and well History of chronic GVHD Off all medications Karnofsky score = 100%	6	5
Mild to moderate disability from chronic GVHD On medications for chronic GVHD Karnofsky score = 90%	2	1
Mild to moderate disability No history of chronic GVHD Karnofsky kscore = 90%	2	1
Total no. of survivors	20	22

*Groups are designated by the TBI regimen.

Previous studies have demonstrated that a combination of MTX and CSP is effective in preventing GVHD and its associated mortality. Attempts to use this information require the use of chemotherapy and radiotherapy regimens that permit the effective delivery of this form of prophylaxis and are effective in preventing posttransplant relapse. The TBI regimens described in the present report are each more effective with respect to one of these objectives, and less effective with respect to the other. Alternative regimens to accomplish both goals may be 14.0 Gy TBI administered over 7 days or 13.50 Gy given over 6 days. Previous studies confirm that these are tolerable doses but the impact on relapse probability in this setting remains to be determined.

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