Total Body Irradiation for Allogeneic Bone Marrow Transplantation in Chronic Myelogenous Leukemia*

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= Abstract =

Between July 1987 and December 1992, we treated 22 patients with chronic myelogenous leukemia; 14 in the chronic phase and 8 with more advanced disease. All were received with allogeneic bone marrow transplantation from HLA-identical sibling donors after a total body irradiation(TBI) cyclophosphamide conditioning regimen. Patients were non-randomly assigned to either 1200 cGy/6fractions/3days (6 patients) or 1320 cGy/8 fractions/4days (16 patients) by dose of TBI. Of the 22 patients, 8 were prepared with cyclophosphamide alone, 14 were conditioned with additional adriamycin or daunorubicin. To prevent graft versus host disease, cyclosporine was given either alone or in conjunction with methotrexate. The actuarial survival and leukemic-free survival at four years were 58.5 % and 41.2%, respectively, and the relapse rate was 36% among 22 patients. There was a statistically significant difference in survival between the patients in chronic phase and more advanced phase (76% vs 33%, $p=0.05$). The relapse rate of patients receiving splenectomy was higher than that of patients receiving splenic irradiation (50% vs 0%, $p=0.04$). We conclude that the probability of cure is highest if transplantation is performed while the patient remains in the chronic phase.

Key Words : Chronic myelogenous leukemia, Total body irradiation, Allogeneic bone marrow transplantation

INTRODUCTION

Bone marrow transplantation (BMT) employing HLA-identical donors in the chronic phase of chronic myelogenous leukemia (CML) currently offers the only significant chance of cure of this disease. It has been suggested that about 50% of patients who received allografts in the early 1980s appear to be cured, and with subsequent advances , it has been anticipated that the cure rate will be even higher for patients transplanted in the 1990s[1~3].

Prolonged disease-free survival can be achieved by marrow transplantation during any phase of the disease, but the best results have occurred when transplantation was carried out during the chronic phase. The probability of survival at 5 years after allogeneic

transplantation from HLA-identical donors is 60 % for patients who receive transplants in chronic phase, 22% for patients in accelerated phase, and 13% for those in blast phase.

Assessment of the relative importance of various pretransplant patient characteristics and of peritransplant events in outcome of marrow transplantation for CML is of immense importance to patients and to counseling physicians[4-6]. In this report, we examine results of a clinical trial testing a uniform bone marrow transplantation preparative regimen and a uniform approach to graft-vs-host disease (GVHD) prophylaxis in the treatment of CML , and we analyze patient characteristics bearing on outcome of transplantation.

MATERIALS AND METHODS

Patient Population

Between July 1987 and December 1992, 22 patients with CML in chronic, accelerated or blast phase received allogeneic bone marrow transplants from HLA-identical siblings in St. Mary's hospital. During the week preceding transplantation, hematologic and cytogenetic studies were repeated so that disease status could be classified as accurately as possible. Patients were assigned to Group A if they were in the first chronic phase, or to Group B if they were in the accelerated, blastic transformation, second chronic phase(after successful treatment of blastic transformation), or secondary chronic phase(after presentation with Ph1-positive acute lymphoblastic leukemia). The recognition of chronic phase was based in general on criteria defined by the International Bone Marrow Transplant Registry[7]; thrombocytosis in excess of 1000×10^9/l was generally regarded as consistent with chronic phase disease. The criteria for recognizing accelerated disease are imprecise, but in making this diagnosis we relied particularly on the presence of inappropriate splenomegaly, usually with blast cells in excess of 10 percent in the blood or marrow, or the presence of cytogenetic changes in addition to the Ph1 chromosome[10]. Fourteen patients were grafted in first chronic phase (Group A), and eight were grafted for more advanced disease (Group B) according to the criteria of the International Bone Marrow Transplant Registry (IBMTR)[7]. The median age of recipients was 30.5 years and the distribution according to recipient sex was 16 males and 6 females. Mean time from diagnosis to BMT was 10 months (range; 4 to 36 months). Patient characteristics are depicted in Table 1.

Table 1. Clinical Features of 22 Patients with Chronic Myelogenous Leukemia

	Group A (Chronic phase)	Group B (Accelerated or Blastic phase)
No of patients	14	8
Sex(M/F)	10/4	6/2
Age(median, yr)	32	28
Interval from diagnosis to BMT (median, mos)	7	14.5
Treatment of spleen		
splenectomy	9	5
splenic RT	4	2
Donor age(median, yr)	29	32.5
Donor/recipient sex		
M/M	4	4
M/F	3	-
F/M	6	2
F/F	1	2
ABO match		
Yes	8	3
No	6	5
Conditioning regimen		
CTX	6	2
CTX+DNR	1	4
CTX+ADR	7	2
1200 cGy HTBI	3	3
1320 cGy HTBI	11	5
GVHD prophylaxis		
MTX+CSA	12	6
CSA	2	2

Preparative Regimens

All the patients were prepared for bone

marrow transplantation with hyperfractionated total body irradiation (HTBI) followed by chemotherapy (HTBI ; D-7 or -6 to D-4, chemotherapy; D-3, -2). Total body irradiation was administered bilaterally using 6 MV linear accelerator at a dose rate of approximately 8 to 12 cGy per minute. Patients were non-randomly assigned to either 1320cGy or 1200cGy. For 16 patients, irradiation regimen was 1320 cGy in eight fractions for four days (165 cGy twice daily), and for 6 patients, 1200 cGy in six fractions for three days (200 cGy twice daily) at a source-axis distance 380 -400cm with or without lung and lens shielding. Details of the treatment technique and dosimetry are described in reference[8,9]. The conditioning regimen included cyclophosphamide (CTX, 60 mg/kg) for all patients. Additional chemotherapy was delivered for 9 patients with adriamycin and for 5 patients with daunorubicine (60 mg per square meter of body surface area).

Treatment of the Spleen

All patients in this series either underwent splenectomy (14 patients) or received additional irradiation to the spleen (8 patients, 250 to 800 cGy/2-8 fractions) before transplantation.

Bone Marrow Donors

Donors and recipients were identical for HLA. The donors had a median age of 32 years (range, 13 to 42);11 were male, and 11 female. Of the 16 male patients , 8 had male donors and 8 had female donors; of the 6 female patients, 3 had female donors and 3 had male donors. Analysis of donor/recipient pairs revealed that 50% were sex mismatched and 50% ABO mismatched BMT.

Prevention of Graft versus Host Disease

Prophylaxis of acute graft versus host disease (GVHD) was systematically prescribed and consisted of either methotrexate (MTX) and cyclosporine (CSA) (18 patients) or CSA (4 patients) as described by the Seattle team[5]. All the patients were transplanted with non-T cell depleted bone marrow.

Statistical Analysis

Survivals were calculated by Kaplan-Meier method and significance was estimated by the Log rank test, and Fisher's exact test. Survival and relapse data were analysed as of July 1993. The median follow-up is 25 months (range; 2 to 69 months).

RESULTS

Survival

The actuarial survival was 58.5% at 4 years, and the four year leukemic-free survival was 41.2% among 22 patients. Figure 1 shows the probability of survival for patients receiving transplants in the chronic and accelerated or blastic phases. The survival of patients receiving transplants in the chronic phase is significantly better than that of patients receiving transplants in the accelerated or blastic phases (76% vs 33%, p=0.05). When the patients were divided into two age groups-those 30 years old or younger, and those 31 years old and older-the younger patients had an actuarial survival inferior to that of older patients (46% vs 72%). The difference was not statistically significant. Survival among patients receiving

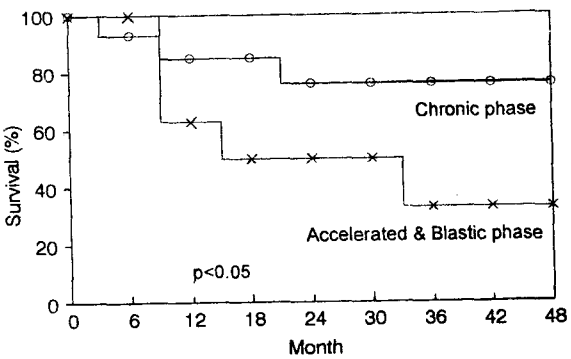

Fig. 1. Survival after BMT according to Disease phase

Table 2. Variables Examined for Associations with Probability of Relapse and Survival in Univariate Analysis

Variables	No. of patients	Relapse		Survival	
		%	p-value*	%	p-value+
Patient age, yrs					
≤ 30	11	27	0.909	46	0.4758
> 30	11	45		72	
Sex					
male	16	38	0.631	51	0.2872
female	6	33		83	
Interval between Dx and BMT, mos					
≤15	16	44	0.255	61	0.3574
>15	6	17		50	
Spleen status					
splenectomy	14	50	0.044	53	0.8393
spleen irradiation	6	0		50	
Donor age, yrs					
≤30	10	27	0.909	58	0.7847
>30	12	45		55	
Donor sex					
male	11			62	0.2792
female	11			53	
Donor-recipient sex match					
Yes	11	55	0.091	53	0.8413
No	11	18		62	
ABO match					
Yes	11	45	0.330	64	0.3207
No	11	27		55	
Conditionoing chemotherapy					
CTX	8	50	0.291	63	0.8444
CTX+DNR or ADR	14	29		53	
Total dose of radiation, cGy					
1200	6	17	0.960	67	0.6274
1320	16	44		51	
Treatment to prevent GVHD					
MTX+CSA	18	44	0.137	44	0.0861
CSA	4	0		100	
AGVHD					
None	11	36	0.670	68	0.1758
mild to severe	4	36		53	
CGVHD					
None	19	37	0.709	61	0.6204
mild to severe	3	33		67	
Disease phase at BMT					
chronic phase	14	43	0.358	76	0.0550
accelerated or blastic phase	8	25		33	

* Fisher's exact test
\+ Log-rank test

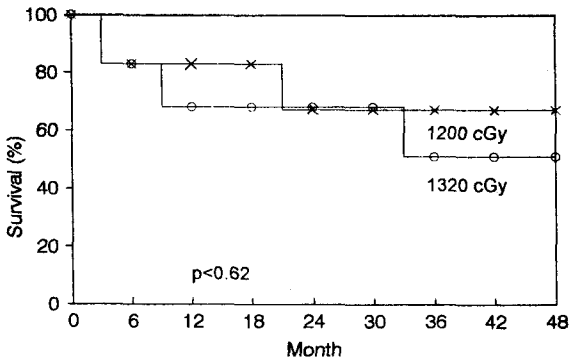

Fig. 2. Survival after BMT according to TBI dose

transplants within 15 months of diagnosis was slightly better than that of patients receiving transplants more than 15 months after diagnosis (61% vs 50%). This difference also was not significant. There was no difference in survival between patients who underwent splenectomy and those who received splenic irradiation (53% vs 50%, $p=0.83$). The survival according to whether or not they developed GVHD has not showed statistically significant difference (45% vs 78%, $p=0.20$). There was no significant difference in survival between those who received MTX and CSA and those who CSA alone for prevention of GVHD (44% vs 100%, $p=0.08$). Female patients had an actuarial survival superior to that of male , but the difference was not statistically significant (51% vs 83%, $p=0.29$). Survival among patients receiving CTX alone was not statistically different from that of patients receiving combined chemotherapy (63% vs 53%, $p=0.84$). We could not demonstrate any statistically significant difference in overall survival nor in disease-free survival between the two 1200 cGy and 1320 cGy groups (67% vs 51%, $p=0.63$, Fig. 2). Fifty percent of patients received a transplant from a donor of the same sex and/or ABO type, but there was no statistical significance among their survival. Table 2 shows the variables examined for association with probability of relapse and survival in univariate analysis.

Table 3. Factors associated with GVHD

Factor	Incidence of GVHD(%)	p-value
Patient age ≤30	63	0.500
>30	54	
Donor age ≤30	50	0.890
>30	66	
Donor-recipient sex match		
Yes	63	0.500
No	54	
ABO match		
Yes	54	0.807
No	63	
Conditioning regimen		
CTX	25	0.999
CTX+DNR or ADR	78	
1200 cGy	50	0.845
1320 cGy	62	
Spleen status		
Splenectomy	64	0.455
Splenic RT	50	
GVHD prophylaxis		
MTX+CSA	55	0.902
CSA	75	

Relapse

Among 22 patients, 4 patients developed engraftment failure and 8 patients had relapse with 36% relapse rate. Four of relapsed patients have survived after treatment with interferon. Univariate analyses were performed to assess the influence of various presenting features on relapse(Table 2). Only spleen status correlated significantly with relapse. In this series, the development of GVHD could not be associated with protection from relapse.

GVHD

Acute and chronic GVHD developed in 13 of 22 patients. Various potential factors for GVHD were studied: patient and donor age, spleen status, donor/recipient sex and ABO match, conditioning chemotherapy, TBI dose,

Table 4. Primary Causes of Death

Cause	No of patients
Relapse	4
Engraftment failure	3
TTP+ like syndrome	1
Bronchiolitis obliterans	1*

+ Thrombotic thrombocytopenic purpura
* Consistent with relapse

and prophylaxis of GVHD (Table 3).

Complication

There was only one case of interstitial pneumonitis occurring within 2 months after transplantation in 1320 cGy group. The patient died of engraftment failure. The other complications noted were : herpes zoster(3), multiorgan failure(1), sepsis(1), hemolytic anemia(1), thrombotic thrombocytopenic purpura(TTP, 1).

Cause of Death

Eight of 22 patients have died, and the primary causes of death are given in Table 4. In 4 cases, leukemic relapse was a prominent clinical feature at time of death, one of these had a pathological changes consistent with bronchiolitis obliterans. Three additional patients died of engraftment failure and one death was attributed to TTP-like syndrome.

DISCUSSION

Most teams worldwide have used cyclophosphamide and TBI as preparation for the marrow graft, as described in recent papers of the IBMTR and of the Seattle Team[5,7,11]. The goals of TBI in allogeneic BMT are: to contribute in eradicating the leukemia cells; to contribute in immunosuppressing the recipient ; to contribute in providing space for the transplant, and this has to be done without exceeding the tolerance limits of critical organs: lung, gut, kidney, lens, etc. There is now convincing evidence that patients with CML can be cured by BMT at any stage of the disease [5-7, 11-14]. Partly because no other method of treating CML offers any realistic prospect of cure, CML has now become the major indication for allogeneic BMT. The major determinants of success or failure are the phase of the disease when transplant is undertaken, the age of the patients, and the incidence of GVHD. Initially, TBI was given as a single dose at a low dose rate. It is well established that, for a given dose, the degree of biological damage from radiation increases with increasing dose rate. Data from the IBMTR have shown that, for single fraction TBI, there is a significant increase in the incidence of interstitial pneumonitis for dose rates above 4 cGy/min[15]. Corvo et al. found a correlation between dose and relapse rate: 50% of patients with CML relapsed with a TBI dose of less than 990 cGy, compared to 0% with doses above 990 cGy[16]. Peters et al proposed, on radiobiological grounds, that fractionated TBI would improve lung tolerance for a given bone marrow cell kill relative to a single dose at high dose rate[17]. The single most devastating problem following BMT is interstitial pneumonitis. Interstitial pneumonitis is characterized by interstitial pulmonary infiltrates on chest X-ray. It may develop within weeks or months after BMT and is frequently fatal. In Seattle study, 13 of 49 (26%) of patients conditioned with CTX and single fraction TBI, died of interstitial pneumonitis[18]. This is further emphasized by data from the IBMTR, showing that in 932 patients undergoing BMT, 920 of whom received TBI, the incidence of interstitial pneumonitis was 29% with a fatality rate of 84%[15].

There is now a general agreement that cure can be achieved in a relatively high proportion of CML patients under the age of 50 years if the transplant is carried out in chronic phase. The Seattle group shows an improvement of the results if BMT is carried out during the first year of diagnosis[5]. The overall results show a 4-year disease-free survival of 50%

with a risk of relapse of 75%[11]. If, however, the transplant is delayed until the patient has entered the accelerated or the blastic phases of CML, then the corresponding figures for probability of relapse (about 50%) and survival (15 to 25%) are much poorer[12]. This reflects both the relative resistance to eradication of the transformed leukemia cells and the higher incidence of transplant-related mortality in patients with non-chronic phase of the disease. A myelo-ablative regimen including CTX and TBI gives a high percentage of bone marrow take in allogeneic HLA identical bone marrow transplantation. T cell depletion or other methods of preventing GVHD has increased the number of relapses, showing that the anti-leukemic effect of BMT was not only due to the intensity of the conditioning regimen but also to the graft versus leukemia effect of allogeneic T lymphocytes. Attempts at increasing the conditioning regimen by adding other drugs or by modifying the fractionation and the total dose of irradiation did not improve markedly the overall survival because of the increase of toxicity. Comparison of busulfan and TBI as a conditioning regimen is currently undertaken in prospective randomized studies. Preliminary results show that the combination of busulfan and CTX seems to be a good alternative to TBI. The question whether the combination of MTX-CSA is associated with a higher rate of leukemia relapse in comparison with either agent alone is controversial[19]. In this respect, no evidence was found that combined therapy causes more relapses than CSA alone in a recent report from Seattle[20]. Altering drug and radiation doses and schedules may not substantially improve transplantation results.

In this retrospective study of 22 patients with CML who received an unmanipulated, non-T-cell depleted marrow graft from an HLA identical sibling donor, TBI schedule apparently does not dramatically modify the clinical outcome of patients. Today, a TBI regimen can be designed on the basis of radiobiological data emerging from experimental works and clinical experiences but clinical tests for solid confirmation are strongly needed.

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=국문초록=

만성 골수성 백혈병에서 동종 골수 이식을 위한 전신방사선조사

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목 적 : 1987년 7월부터 1992년 12월까지 가톨릭의과대학 부속 성모병원 치료방사선과에서 만성골수성백혈병으로 진단되어 동종골수이식을 위한 전신방사선치료를 받은 환자 22명을 대상으로 생존율 및 재발율에 영향을 미치는 요소들을 알아보기 위하여 후향분석을 시행하였다.

대상 및 방법 : 22명중 14명은 만성기였으며 8명은 이행기 혹은 급전기였고 진단 후 골수이식까지의 기간은 4-36개월 (중간값, 8개월)이었으며, 모든 환자들은 HLA 완전일치의 동종골수이식을 위한 전처치로 화학요법과 전신방사선조사가 시행되었다.

전신방사선조사는 6예에서는 1200cGy/6 fractions/3days, 16예에서는 1320cGy/8fractions/4days로 시행되었다. 화학요법은 8명에서는 cyclophosphamide(CTX), 5명에서는 CTX과 Daunorubicin, 그리고 9명에서는 CTX과 Adriamycin이 병용되었다. 또한 골수이식전 비장이 절제된 경우는 14예였고 6예에서는 비장에 방사선조사 (250-800 cGy/2-8fractions)가 시행되었으며 2예에서는 비장 방사선조사후 비장절제술이 시행되었다.

이식편대숙주병을 예방하기 위해 4명에서는 cyclosporine A가 단독투여되었고 18명에서는 methotrexate가 추가 투여되었다.

결 과 : 전체환자의 4년 생존율은 58.8%였고 22명중 8명이 재발되었으며 4년 무병생존율은 41.2%였다. 생존율 및 재발율, 이식편대숙주병에 있어서 환자의 성별, 연령, 진단에서 골수이식까지의 기간, 골수이식 당시의 병기, 비장상태, 골수공여자와의 성별 혹은 혈액형 일치여부, 골수 공여자의 연령, 전처치 항암제의 종류, 방사선치료방법, 이식편대숙주병의 억제를 위한 화학요법의 방법 등이 어떤 영향을 미치는지 분석한 결과 골수이식당시의 병기만이 생존율에 유의한 차이를 보였다. 또한 이식편대숙주병과 재발율 사이에도 유의한 연관성을 보이지 않았다.

결론적으로 동종골수이식을 위한 전처치 및 면역억제방법에 따라 생존율 및 재발율이 크게 다르지 않았으며 HLA 일치 혈연자중 골수공여자가 있는 만성기의 만성골수성 백혈병 환자에서 동종골수이식을 위한 전처치로서 화학요법과 함께 전신방사선 분할조사는 중요한 역할을 담당함을 알 수 있었으나 보다 많은 환자를 대상으로 한 전향적 연구가 필요할 것으로 사료된다.