Total Body Irradiation in Leukemia

— Preliminary Report —

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Total body irradiation has been applied to treat acute leukemia and chronic granulocytic leukemia. 20 patients with acute leukemia or chronic granulocytic leukemia were treated with total body irradiation using 6 MV linear accelerator before bone marrow transplantation at the Division of Therapeutic Radiology, Department of Radiology, St. Mary's Hospital, Catholic University Medical College from August 1987 to September 1988.

Among 20 patients, 8 patients received 6 fractions of 200 cGy (total 1200 cGy), 10 patients received a single 850 cGy radiation, 1 patient received 4 fractions totalling 850 cGy (200, 200, 200, 250), and 1 patient received 1100 cGy in 2 fractions (850, 250). 17 patients received allogenic grafts, 2 patients received autologous grafts, and only one patient received one locus mismatched graft. 13 patients are still alive and 7 patients died. The complications induced by total body irradiation were nausea and vomiting, diarrhea, skin erruption, mucositis, and pneumonitis.

Key Words: Total body irradiation, Leukemia, Bone marrow transplantation

INTRODUCTION

Allogeneic bone marrow transplantation has developed into an long effective therapy for patients with hematologic malignancies and may lead to their longterm disease-free survival. Prior to bone marrow transplantation, patients generally require conditioning therapy. Currently used protocols include single or multiple chemotherapeutic agents in high concentrations and total body irradiation delivered by various techniques[1,2].

Since 1969, whole body irradiation (total body irradiation, TBI) has been used routinely to treat patients with leukemia undergoing bone marrow transplantation[3]. This conditioning therapy must suppress the recipient's immunity sufficiently to allow sustained engraftment and prevent rejection of the transplant.

When the transplant is used for treatment of malignancy, this therapy must also completely eradicate the neoplastic cells. The transplant procedure involves intravenous infusion of recipient bone marrow. These cells are collected from the donor by multiple bone marrow aspirations. The donor bone marrow cells engraft and establish normal hematopoiesis in the recipient, usually within 3 to 4 weeks. Post-transplant immunosuppressive treatment is typically administered with the objective of preventing or modifying graft versus host disease.

Intensive chemotherapy, total body irradiation, and bone marrow transplantation may be associated with a number of complications. These include toxicity of the pretransplant treatment regimen, graft rejection, posttransplant immunodeficiency, infections and interstitial pneumonitis.

RATIENTS AND METHODS

1. Patients

Between August 1987 and September 1988, 20 patients with leukemia were treated with combinations of cytotoxic drugs at high dosage, total body irradiation and infusion of hematopoietic stem cells. Their diagnoses and type of graft at the time

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of transplantation are shown in table 1. 17 patients had acute leukemia, and 3 patients had chronic leukemia. 17 patients were allografted with bone marrow cells from HLA-identical sibs, 2 received reconstituted autologous nucleated blood cells which had been collected and cryopreserved at or soon after original diagnosis. Only one patient received one locus mismatched graft. 7 patients had Ist complete remission, 4 patients were Ist relapsed, 6 patients were diagnosed as 2nd relapse and the number of patients with 2nd complete remission was 1 patient (Table 2).

2. Technique for Total Body Irradiation

The schedule of total body irradiation varied slightly for different patients. The radiotherapy technique use 6 MV x-rays, bilateral opposing fields, and individualized compensators. When the fractionation irradiation. The Ist treatment was usually given on a Monday at 8.30 h followed by the second one at about 16.30 h on the same day making an interval of about 8 h between the Ist two fractions.

Subsequent fractions were given at the same times in the morning and afternoon on the following days. The overall time per fraction, including setting-up time, was about 30 min. This treatment schedule reduced to a minimum any interference with the daily program of other patients receiving radiotherapy[4,5].

Among 20 patients, 8 patients received 6 fractionations each of 200 cGy (Total 1200 cGy), 10 patients received a single 800 or 850 radiation, 1 patient received 4 fractions totalling 850 cGy (200, 200, 200, 250), and 1 patient received 2 fractionated 1100 cGy (850, 250).

Table 1. Patient Distribution by Type of Graft

Diagnosis	Type of graft	No. of patients
ALL	Autograft	1
	Allograft	7
AML	Autograft	1
	Allogarft	7
	Mismatched	1
CML	Allograft	3

Table 2. Patient Distribution by Timming of Total Body Irradiation

Diagnosis	Hematologic status	No. of patients
ALL	DMPS*	1
	1st relapse	3
	2nd relapse	3
	2nd CR	1
	4th CR	1
AML	1st CR	7
	1st relapse	1
	2nd relapse	1
CML	1st relapse	1
	2nd relapse	2

* DMPS : Preleukemic status

RESULTS

1. Anti-leukemia Effect of Irradiation

13 patients are alive and their mean survival is 7.5 months. 7 patients died and their mean survival was 3.3 months. Of the 7 patients who died, 2 of those died in relapse of acute leukemia or of blastic transformation of chronic granulocytic leukemia. But 5 patients died of complications of the transplant procedure with evidence of leukemia.

These included Grade IV graft versus host disease (2 cases); meningitis associated with pneumococcal infection (1 case); acute renal failure with hypomagnesemia (1 case); and cardiac

Table 3. The Characteristics of Survival Patients

Patient No.	Diagnosis	Timming of TBI	Survival
1	AML	1st CR	13 months
2	ALL	2nd relapse	12 months
3	CML	2nd relapse	11 months
4	AML	1st CR	10 months
5	ALL	1st relapse	8 months
6	CML	1st relapse	8 months
7	AML	1st Cr	9 months
8	CML	2nd relapse	5 months
9	AML	1st CR	5 months
10	ALL	2nd relapse	5 months
11	ALL	DMPS*	4 months
12	ALL	2nd CR	3 months
13	AML	1st CR	3 months

* DMPS : Preleukemic status

Table 4. Cause of Death

Dingnosis	ENGR*	REJ**	Cause of death	Survival
ALL, 4th CR	Yes	No	Relapse	3 months
ALL, 1st reapse	Yes	No	Meningitis	12 months
AML, 1st CR	Yes	No	Relapse	4 months
ALL, 2nd relapse	Yes	No	ARF***	1 month
AML, 1st relape	Yse	No	GVHD****	1 month
AML, 1st CR	Yes	No	GVHD	2 months
AML, 2nd relapse	Yes	No	Pul. edema	7 days

* ENGR : engraftment
** REJ : rejection
*** ARF : acute renal failure
**** GVHD : graft versus host disease

toxicity with pulmonary congestion associated with presumed toxicity of chemotherapy (1 case)(Table 4).

2. Complications of Irradiation

The majority of patients experienced nausea vomiting as a result of treatment with cytotoxic drugs, immediately before total body irradiation. In almost every case symptoms had subsided completely after total body irradiation.

After total body irradiation was completed, 13 patients had some degree of mucositis involving buccal mucous membrane and/or oropharyngus; 11 patients had diarrhea with increasing frequency of loose bowel actions. 7 patients experienced skin rash and erythema especially on the neck and upper chest area (Table 5).

In no case was the schedule of total body irradiation altered or interruped as a result of toxicity. These symptoms were attributed in part to the total body irradiation and in part to the preceding cytotoxic drugs. 4 patients had pulmonary complications. 7 patients had viral infection, and 3 patients had fungal infection. Among them 2 patients experienced septicemia. In each case total body irradiation might or might not have been an important factor contributing pulmonary complication and several infections[6,7].

Table 5. Treatment Complications

Complication	No. of patients	Percentage (%)
Nausea & vomiting	12	40
Diarrhea	16	53
Rash	7	23
Mucositis	13	43
Pneumonia	4	13
Viral infection	6	19
Septicemia	2	7
Fungal infection	2	7
Cardiac toxicity	1	3

DISCUSSION

Bone marrow transplantation is increasingly employed to treat patients with acute and chronic leukemias. total body irradiation is a regular but not universal component of treatment before marrow transplantation for patients with leukemia. In the treatment of most solid tumors, radiotherapy is administered in multiple fractions, because repair of normal tissues between fractions proceeds more efficiently than repair of malignant tissues. Since the total effective dose of total body irradiation is limited mainly by its potential toxicity to normal tissues, especially the lungs, the critical question in leukemia is whether repair mechanisms in normal pulmonary tissues are more efficient than in leukemic cell populations[8].

In practice the capacity of tissues for repair following irradiation can be deduced in part from assessment of the "shoulder" in the radiobiological dose response curve. It is assumed that a substantial shoulder reflects considerable capacity for repair when cells are exposed to relatively low radiation doses, whereas a small shoulder is interpreted as indicating that little repair can take place.

With these criteria, some dose-response experiments suggest that hemopoietic tissues, both normal and neoplastic have relatively small shoulders compared with lung tissues[9].

This would be an excellent radiobiological basis

for fractionating the total body irradiation to permit administration of higher doses which might augment the antileukemic effect with relative sparing of the lung.

The total of irradiation necessary to eradicate residual leukemic cells in a given patient is not known. The appropriate dose is probably determined in part by factors unique to the biology of the disease in an individual patient and in part by the size of the leukemic cell mass persisting after treatment.

Moreover the radiobiological equivalence of radiotherapy given as a single dose and as fractionated doses is not accurately known. Nevertheless, it seems clear that toxicity to the lungs limits the amount of total body irradiation that can in practice be administered-- pulmonary toxicity or idiopathic interstitial pneumonitis seems to be related to absorbed radiation dose to lung[10] and is rare at total doses below 800 cGy; at total doses above 800 cGy the incidence of interstitial pneumonitis rises sharply and seems then to be related to the rate at which radiotherapy is administered[11].

The Seattle group has recently reported a study in which patients undergoing treatment for leukemia received total body irradiation either as a single dose of 1000 cGy administered from dual opposed cobalt sources at a dose rate of 8 cGy/min or as 1200 cGy in 6 daily fractions each of 200 cGy[12].

The authors were unable to recognize any significant differences in immediate toxicity or in antileukemic effect of the two regimens but the preliminary analysis showed superior survival for patients treated with fractionated total body irradiation.

Our study must be emphasized that the follow-up of our patients is relatively short and further late toxicity may still be encountered. From the patient's point of view fractionated total body irradiation certainly seemed more acceptable. Moreover such treatment could be accommodated in the routine workload of a radiotherapy department more easily than treatment given as a single dose.

It seems therefore to be the method of choice provided the antileukemic and immunosuppressive effects are not thereby diminished.

CONCLUSION

The retrospective analysis of the total body irradiation for the acute leukemia, chronic granulocytic leukemia in 20 patients between August 1987 and Septmber 1988 at Department of Radiology, Catholic University Medical college.

The results were as followings;

1. 13 patients are still alive, and 7 patients died.
2. The mean survival of alive patients is 7.5 months.
3. The causes of death were relapse, graft versus host disease, meningitis, acute renal failure, and pulmonary edema.
4. The complications were diarrhea, mucositis, nausea, vomiting, rash, viral infection, pneumonia, septicemia, fungal infection, and cardiac toxicity.

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= 국문초록 =

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1987년 8월부터 1988년 월까지 가톨릭의대 부속 성모병원 방사선과에서는 20명의 급성 백혈병 환자와 만성과립성 백혈병 환자를 6 MV 선형가속기를 사용하여 전신조사 하였다. 20명의 환자중 8명은 총 방사선량 1200 cGy씩 1회 방사선 조사를 받았다. 나머지 2명 중 1명은 4회 분할 조사로 총 850 cGy를 받았으며, 다른 1명은 2회 분할 조사하여 총 1100 cGy를 받았다. 이식편은 20명중 17명이 동종 이식편을 받았고, 2명이 자가 이식편을 받았으며, 오직 1명만이 부적합 이식편을 받았다. 현재 13명이 생존해 있고, 7명이 사망 했으며, 전신조사에 의한 합병증은 설사, 점막염증, 구토와 구역, 피부발진 등의 순으로 나타났다.