

# Bone Marrow Transplantation in Ramathibodi Hospital : Progress Report

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High dose chemotherapy or chemoradiotherapy followed by bone marrow transplantation (BMT) is now used to treat a wide range of hematological disorders. Patients with acute non-lymphoblastic leukemia (ANLL) in the first chemotherapy induced remission who underwent marrow transplantation survived better than those given chemotherapy alone (50% vs 20% actuarial survival rates at 8 years).<sup>1</sup> Patients with acute lymphoblastic leukemia (ALL) who received bone marrow transplant in second or subsequent remissions have a survival rate of approximately 35% at 8 years whereas similar patients undergoing chemotherapy have all died of recurrent disease within 3 years of the initiation of therapy.<sup>2</sup> Bone marrow transplantation has been the only hope of cure for patients with chronic myelocytic leukemia.<sup>3,4</sup> In Burkitt's lymphoma, despite the acute sensitivity of the tumor to both chemotherapy and radiotherapy, the outcome in advanced or disseminated disease was poor.<sup>5,6</sup> In relapsed patients, long-term survival was almost unknown. Massive chemotherapy followed by autologous BMT can offer long term survival and probable cure in selected patients.

**SUMMARY** Bone marrow transplantation has become the accepted treatment for several hematologic disorders. We have done 3 autologous and 6 allogeneic bone marrow transplantations at Ramathibodi Hospital since July 1989 in patients with acute lymphoblastic leukemia, acute non-lymphocytic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma and severe aplastic anemia. Only one patient with aplastic anemia had late graft rejection, but the rest of them engrafted and did well during the median follow up period of 317 days (range: 39 to 982 days) post transplantation. None of the allogeneic BMT had graft-versus-host disease. We use cyclosporin and short course methotrexate for post transplantation immunosuppression.

<sup>7,8</sup> In patients with aplastic anemia undergoing marrow transplantation, long-term survival rates ranging from 70% to 80% have been observed compared with only a 20% survival rate with supportive therapy and approximately a 50% survival rate with immunosuppression through antithymocyte globulin.<sup>9-11</sup> In Ramathibodi Hospital, we started the BMT Program in July 1989. It is the second BMT center in Thailand. During July 3-November 10, 1989, February 13-April 20, 1990 and February 10, 1991 onwards, we have transplanted 9 cases. The first three cases have already been reported.<sup>12</sup>

## MATERIALS AND METHODS

### Patients

Patients eligible for bone mar-

row transplantation were all in the service of the Division of Hematology of the Department of Medicine and the Department of Pediatrics, Ramathibodi Hospital except for 2 patients that were referred from other teaching hospitals. The patient selection was done through consideration of all the staff in the transplantation team from each department.

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**Conditioning regimens**

Five kinds of conditioning regimens were selected to use in our patients; selection in each individual patient was in according to the disease and appropriate condition. In patient with malignant disease, the regimen were selected among BACT, cyclophosphamide and total body irradiation (TBI), busulfan and cyclophosphamide, and high dose cytosine arabinoside and TBI (Fig. 1, 2, 4 and 5). In patients with severe aplastic anemia, high dose cyclophosphamide alone was used (Fig. 3).

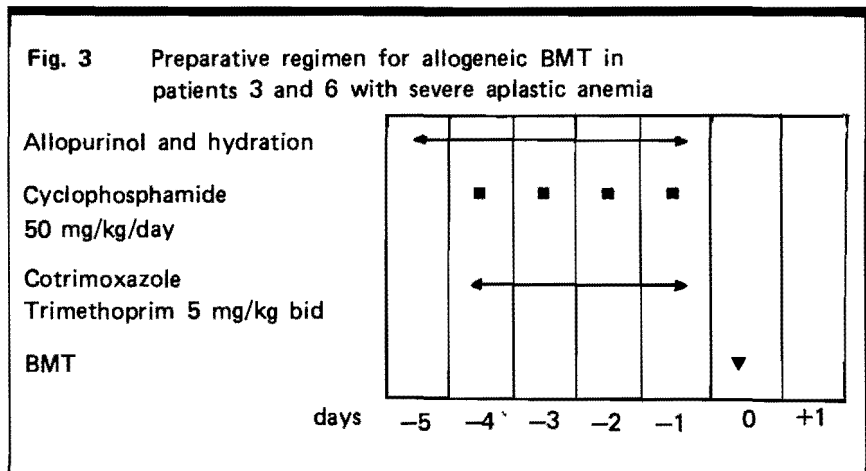
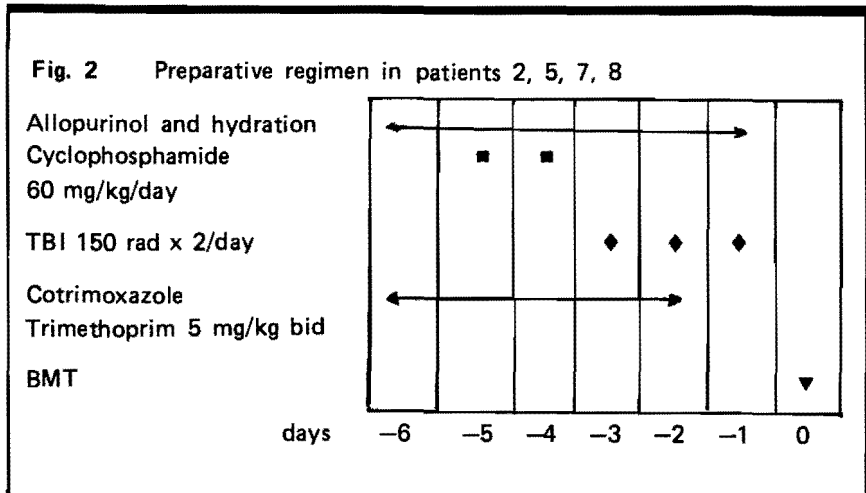
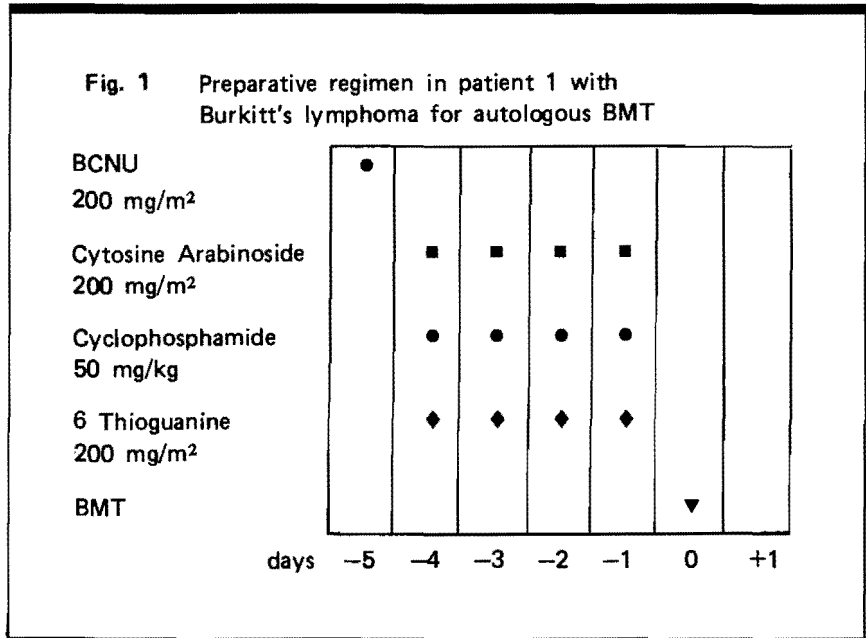
**Bone marrow harvest and transplantation**

Bone marrow donors and recipients were identical for HLA-A, -B, -C and -DR and had negative mixed lymphocyte reaction. Bone marrow was harvested from the donor's posterior superior iliac crests, filtered and infused into the recipient via a central venous catheter immediately thereafter in case of ABO compatible allogeneic BMT. For patients with major ABO incompatibility with the donor, the donor's marrow red blood cells were separated by the cell separator before infusion and the patient received plasmapheresis twice daily 1-2 days before marrow infusion. For autologous BMT, the patients' own marrow mononuclear cells were separated and cryopreserved using a Nicool 10 programmed freezer to -120°C then stored in liquid nitrogen at -190°C. The frozen marrow cells were thawed in 37°C water bath and infused into the patients immediately after thawing.

Cyclosporin and short course of methotrexate were used for prevention of graft versus host disease.<sup>13</sup>

**Informed consent**

All risks of the treatment protocols were fully explained to the patients, donors and relatives. Informed consent was obtained using forms approved by the hospital committee.



**Supportive care**

The patients were given supportive care as previously described.<sup>12</sup>

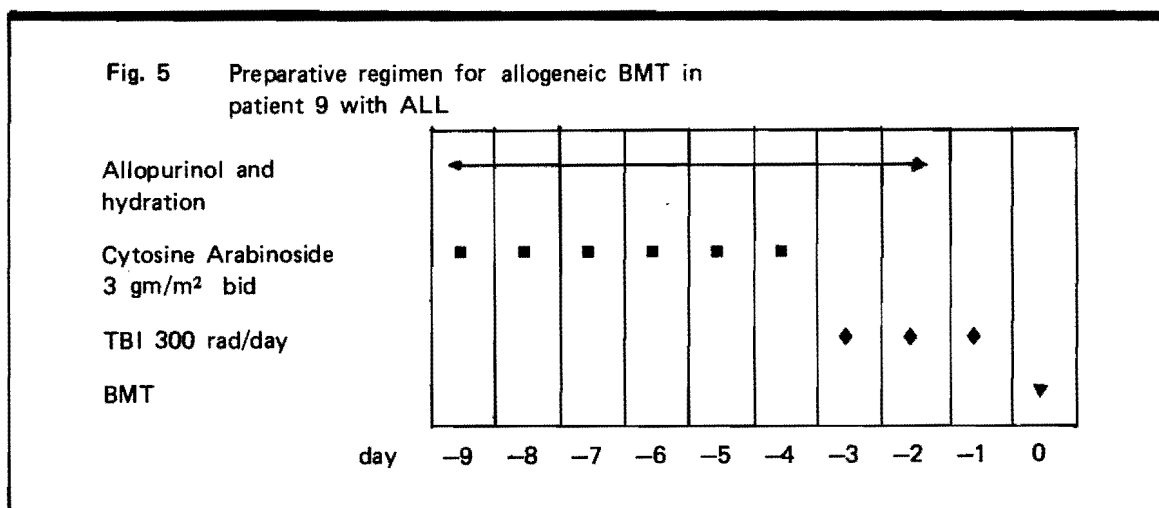
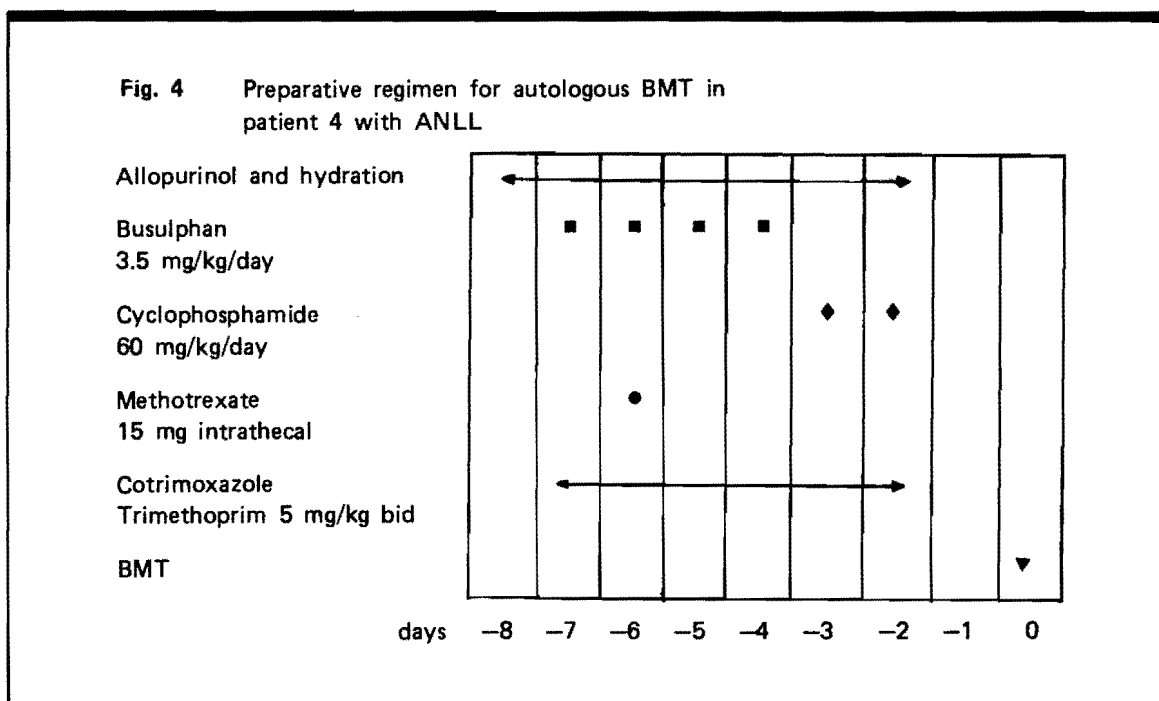
**RESULTS**

Nine patients, aged 9 to 41 years old (median 27 years old) were enrolled in the transplantation program; six were allogeneic and three were autologous. There were two cases of severe aplastic anemia and seven cases of

malignant hematologic diseases (Table 1). The mean number of nucleated cells harvested was  $3.73 \times 10^8$  per kg of the recipient's body weight (range  $1.48 \times 10^8$  to  $5.5 \times 10^8$ /kg). Our median follow up is now 317 days (to March 15, 1992) with the range of 39 to 962 days.

Engraftment was confirmed in each case by a change in ABO blood group, rising white blood cell and

platelet counts and by a change in karyotype (chromosome polymorphism and sex chromosome identification method). According to these criteria, primary graft failure was not encountered; all of our patients demonstrated hematologic recovery ( $PMN > 500/mm^3$ ) and engraftment within 12 to 43 days (median 24 days). All of the patients who were transplanted because of malignant diseases (ANLL, ALL, CML, Burkitt's lym-



**Table 1** Clinical details of 9 patients transplanted

No.	Age(yr)		Diagnosis	Date Diagnosed	Date Transplanted	Type of BMT	Donor Age/sex	ABO group	
	Sex							Donor	Recipient
1	9/M		Burkitt's lymphoma (CR)	Sept 24, 1986	July 27, 1989	Auto	—	—	B
2	32/M		CML (CP)	Feb 1988	Sept 22, 1989	Allo	29 M	A	A
3	29 M		SAA	Feb 1990	Feb 23, 1990	Allo	38 F	B	O
4	27/M		ANLL (CR)	Oct 9, 1990	Feb 19, 1991	Auto	—	—	O
5	26/M		CML (CP)	Dec 4, 1990	May 3, 1991	Allo	28/F	B	B
6	30/M		SAA	May 22, 1991	July 23, 1991	Allo	28/M	A	A
7	41/F		NHL (CR)	Sept 30, 1987	Aug 9, 1991	Auto	—	—	O
8	26/F		CML (CP)	Feb 9, 1989	Sept 13, 1991	Allo	25/F	AB	B
9	18/M		ALL (PR after 2nd relapse)	Sept 1990	Feb 6, 1992	Allo	13/F	A	A

CML = chronic myelocytic leukemia, CR = complete remission, SAA = severe aplastic anemia, PR = partial remission, ANLL = acute nonlymphocytic leukemia, CP = chronic phase, NHL = non Hodgkin's lymphoma, ALL = acute lymphocytic leukemia, Auto = Autologous BMT, Allo = Allogeneic BMT.

**Table 2** Results of the BMT

Patient No.	No. of PRC transfused	No. of Plt conc transfused	Days to achieve		Days of follow up post transplant *	Current performance status (ECOG)
			Wbc >1x10 <sup>9</sup> /l	Neutrophil >0.5x10 <sup>9</sup> /l		
1	1	7	9	12	962+	0
2	3	38	24	24	905+	0
3	7	42	22	25	751+	1**
4	13	131	42	43	390+	0
5	8	124	25	26	317+	0
6	4	45	18	22	256+	0
7	2	140	21	22	219+	2
8	5	63	19	19	184+	0
9	9	75	21	26	39+	0

\* up to March 15, 1992

\*\* late graft rejection on day + 446, \* currently partial recovery of autologous marrow function.

phoma) have not shown any evidence of disease during the time of follow up and thus need no further treatment except for the immunosuppressive agents in the initial 12 months. Two of the patients with aplastic anemia became transfusion independent after their engraftment, the only treatment given after discharge being the immunosuppressive drugs, which are planned to be discontinued within one year (Table 2).

Infectious complication does not seem to be a major problem. Though all the patients got febrile neutropenia and needed broad spectrum antibiotics and amphotericin B, all of them recovered at the time of hematologic recovery. CMV pneumonia and Herpes simplex infection was not encountered. Hence, all of our patients recovered from the transplantation period and got engraftment without serious complication.

Late complications have arisen in only two of nine patients. Patient 3 had late graft rejection on day + 446 post transplant. Currently, he has partial recovery of his own marrow cells and is transfusion independent. This may be explained by the low number of donor cells he received ( $1.48 \times 10^8/\text{kg}$ , compared to the others who received more than  $3 \times 10^8/\text{kg}$ ). The pre-transplant transfusion he received, which determines poor prognostic outcome of BMT in severe aplastic anemia if it is more than 40 units from different donors, was only 3 units of PRC and 12 units of platelet concentrate. Patient 7 had idiopathic interstitial pneumonitis on day + 105 post transplant which required respiratory support, but responded to corticosteroid treatment and now is alive with ECOG performance status 2. The rest of the patients are event free and live with the ECOG performance status 0.

None of the allogeneic bone marrow recipients developed GVHD, either acute, even in the mildest degree, or chronic. Compared to many series of the western countries

in which the incidence of GVHD is about 20-50%,<sup>15,16</sup> our incidence is comparatively low. Furthermore, many centers in Asia such as the ones in Siriraj Hospital,<sup>14</sup> Hong Kong, Taiwan, Malaysia or Japan (personal communication) also experienced a low incidence, suggesting that GVHD may be less encountered in Asian than in Caucasian populations.

## DISCUSSION

Marrow transplantation, a well established therapeutic procedure in western countries and now established in Thailand, offers a hope for cure for many incurable diseases. Our patients consist of many who have the diseases that, without BMT, would not live longer than six months. But now most of our patients are symptom free and return to their normal lives, resuming the careers they had before they contracted the diseases. Although the expense is high for the transplantation period and the immunosuppressive drugs, the patients usually do not need any medication after the immunosuppressive drugs are discontinued within 6 months to one year. The patients who get autologous transplantation may even need no medication after discharge from the transplantation unit. Compared to the conventional therapeutic methods which bring the patient to many periods of neutropenia and thus expose them to the risk of infection without an acceptable chance of cure, marrow transplantation is considered to have better results and is more cost effective. This paper, together with other reports,<sup>12,14</sup> suggests that bone marrow transplantation can be done with favorable success in Thailand.

The limitations of BMT are that the results in the older age group are poor and that it needs HLA identical siblings in cases of allogeneic transplantation. These limitations restrict its use to a small group of patients.

Since techniques in bone marrow transplantation have been developed just during the past two decades, the detailed protocol varies from institution to institution and this may contribute to slightly different outcomes and incidence of complications. One of these examples is that we experienced a lower incidence of Herpes simplex infection than the center at Siriraj Hospital,<sup>14</sup> perhaps due to prophylactic acyclovir. However, our experience has just begun and there are still many unanswered questions. The outcome in each individual disease is to be determined later when the number of the patients who receive transplants in each group is larger. The low incidence of GVHD has to be confirmed and explained and then, if it is true, less immunosuppressive therapy would be required. The use of colony stimulating factors to enhance granulocytic recovery is to be investigated. The age of the patients is one of the important factors that determine the outcome. In the future, if we have more experience with older patients, many diseases which are prevalent in the older age group such as acute non-lymphocytic leukemia and lymphoma will have a greater chance to become candidates for BMT and the scope of its use will be much broader.

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