RESULTS OF ALLOGENIC BONE MARROW TRANSPLANTATION IN CML IN IRAN

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Abstract − Nineteen patients with CML have been transplanted in our Bone Marrow Transplantation (BMT) section since 1991. The mean age of these patients was 26.05 (SD = 9.35). Our conditioning regimen for these patients was cyclophosphamide 60mg/kg for 2 days and busulfan 4mg/kg for 4 consecutive days. Eleven patients are still alive and eight patients died during follow-up ranging from 6 months to 5 years. This review revealed a poor outcome for patients older than 30. There was also a rise in the mortality rate when the interval between diagnosis and BMT was longer than 2 years. In contrast with some previous reports, we found no relationship between spleen size in the pre-transplant period and BMT outcome, however recurrence of CML after BMT correlates strongly with spleen size ($P<0.001$). Cellular recovery ($WBC > 1000$/ml, $PMN > 500$/ml, $PLT > 100000$/ml) correlates directly with spleen size as well ($P<0.05$).
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INTRODUCTION

Chronic myeloid leukemia (CML) s a hematological malignancy characterized by an excessive clonal proliferation of myeloid cells and their progenitors (1). CML is malignancy of pluripotent hematopoietic stem cells which is characterized by panmyelosis and the presence of the philadelphia chromosome. During the chron.c phase, leukocytosis, splenomegaly and systemic symptoms can be controlled with intermittent or continuous treatment with hydroxyurea or busulfan (1), but available chemotherapeutic agents have no selectivity for malignant cells and are incapable of eradicating the disease or delaying transformation to the blastic phase (2).

Recently however, initial treatment with alpha interferon has been reported to control leukocytosis in approximately 80% of patients (3).

Unlike other chemotherapeutic agents that have been commonly used for the treatment of CML, alpha-interferon can suppress the growth of ph-positive cells and allow the re-establishment of diploid hematopoiesis. In one study, 73% of newly diagnosed patients achieved hematological remission and 19% had complete cytogenetic remission. Allogenic bone marrow transplantation (BMT) is an effective treatment for CML. Of patients undergoing BMT during a blastic crisis, approximately 10–20% become long - term survivors and patients in the accelerated phase have a 35-40% chance of 5 years disease free survival; and patients in the chronic phase have a 50-60% chance. The major limitation of allogenic BMT is the risk of transplant - related complications. In all, 20-30% of patients have died from treatment - related complications, like graft versus host disease (GVHD) and infectious complications, within 6 months of the procedure.

The major prognostic factors predicting transplant outcome are the stage of the disease, age, and interval from diagnosis to BMT (4).

Patients who are transplanted in the first year of disease diagnosis and in the chronic phase have a better outcome (5). An age less than 20 years is a good prognostic factor for allogenic BMT (5).

MATERIALS AND METHODS

Nineteen patients, 10 men and 9 women, with CML underwent allogenic bone marrow transplantation from histocompatibility leucocyte

antigen (HLA) identical siblings during the period 1990-96. The mean age of these patients was 26.05 years (SD = 9.35) with a minimum and maximum of 7 and 40 respectively.

All of our patients except one were philadelphia chromosome positive, and all of them except one patient who was in the blastic phase were in a chronic stable phase. The duration of disease in 5 (26.3%) patients was below 12 months, 12 to 24 months in 9 (47.4%), and over 25 months in the remaining 5 (26.3%) patients. Mean pretransplant WBC was 25273 (SD = 22786). Seven patients (36.8%) had been treated by busulfan previously.

All patients were evaluated with regards to their cardiovascular and pulmonary health before transplantation; and viral infectious assessment including hepatitis B, hepatitis C, HIV and CMV was performed. The conditioning regimen was busulfan 4mg/kg for 4 days and cyclophosphamide 60mg/kg for 2 days. The method of isolation was reverse isolation. The mean number of cells transplanted were 3.08×10^8/kg (SD = 0.52) with a minimum of 2.1×10^8/kg and a maximum of 4.2×10^8/kg.

Supportive care, including daily CBC and blood chemistry, and appropriate management of any electrolyte imbalance and infection, was provided after transplantation. Engraftment was documented by WBC and platelet recovery and cytogenic study. Methotraxate 10mg/m^2 on day 1, 3, 6, 11 and cyclosporine 12.5 mg/kg after transplantation were given to prevent acute GVHD (6). Pre-transplant data on our patients are included in Table 1.

Table 1. Pretransplant characteristics

	mean	SD	minimum	maximum
age	24.47	9.74	7	40
WBC	25273	22786	4800	95600
Neutrophil	13144	13284	3200	50000
Platelet	327263	137522	148000	600000
SplenomegalY*	2.84	2.77	0	9

* cm below costal margin

Statistical Methods

Data analysis was performed by comparing means , correlation and regression and t–test. Chi–square test and fisher exact test subsequently when indicated was carried out.

RESULTS

Eleven (57.9%) patients are alive and eight (42.1%) died during half to five years of follow-up. The causes of death were relapse of disease in two patients, acute GVHD in one, sepsis and ARDS in four and VOD (venooclusive disease) in one. Acute GVHD occured in eleven patients: grade one in 3, grade two in 6, grade three in 1 and grade four in 1 of them who died from this complication (Fig. 1).
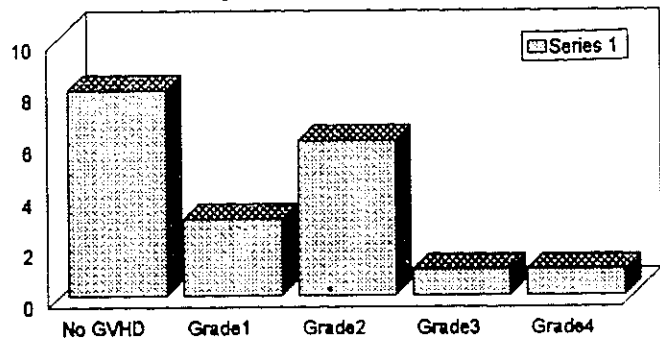

Fig. 1. Acute GVHD Incidence

Acute GVHD occured within a mean interval of 24 days (SD = 11) after transplantation. Recovery of WBC occured within a mean interval of 24.7 (SD = 8.03) and platelet recovery 44 (SD = 21.33) days after transplantation recovery time was defined as post - transplant time to reach WBC > 1000 /ml, PMW > 500 /ml, PLT > 100000 /ml.

There was no statistically significant correlation between the number of cells transplanted and the recovery time for WBC and platelets (this correlation is also documented in our aplastic anemia and thalassemic patients).

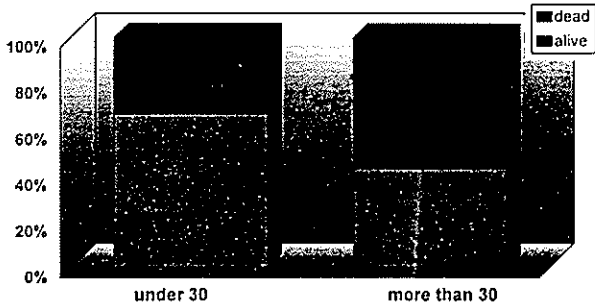Outcome was better in the under age group than in the over-thirty (66.7% versus 42.9%) (Fig.2).

Fig. 2. Effect of age on survival

Fig. 4. Effect of spleen size on WBC recovery

Fig. 5. Effect of spleen size on PLT recovery

This difference is not statistically significant. There was also a rise in the death rate when the interval between diagnosis and BMT was more than 2 years (64% versus 36%) (Fig. 3). In contrast to some previous reports (7 - 8), we found no relationship between size of spleen in the pretransplant period and BMT outcome. In our study however, the mean spleen size in two patients with relapse after BMT, was 7.5cm below costal margin while, it was 1.1 cm in the other non-surviving patients, and 2.3 in the whole group of patients. So it seems that spleen size and recurrence of disease after BMT may be co-relate (p<0.001). Cellular recovery which is defined as WBC>1000/ml, PMN>500/ml, PLT>1000 10/ml correlates directly with spleen size as well (p<0.05), so we can guess a more prolonged WBC and PLT recovery time in patients with larger spleens (Figs. 4, 5).
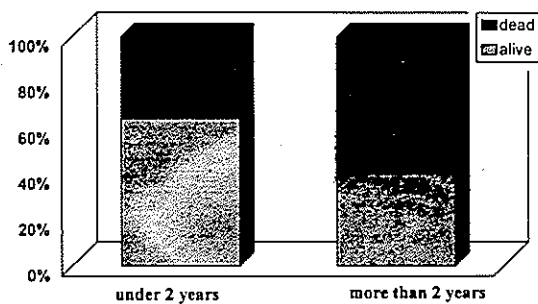
Prior therapy with busulfan was associated with a greater risk of transplant-related mortality (Fisher: 0.06). Five out of seven patients who were treated with busulfan during the chronic phase died from BMT-related complications (71.4%), but mortality in the group which had not been treated with busulfan was 25% (Fig. 6). The survival curve levelled off after 18 months at 59% as is shown in (Fig. 7).

There was no significant statistical relationship between the number of transplanted bone marrow cells and acute GVHD incidence.
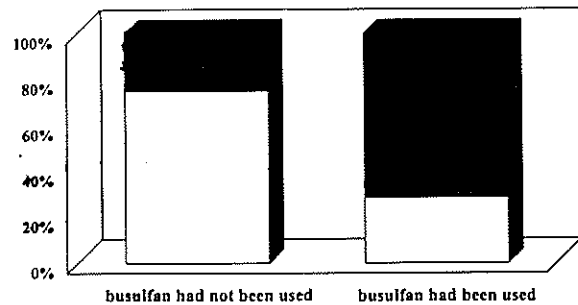

Fig. 3. Effect of duratin of disease on survival

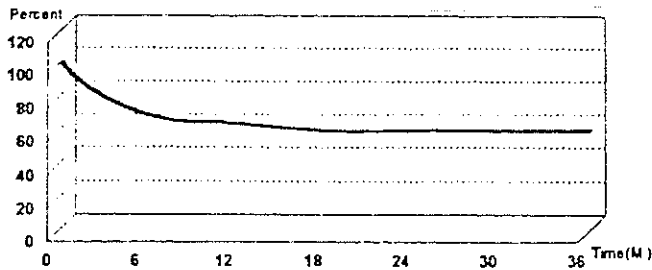Fig. 6. Effect of busulfan on survival

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Fig. 7. Survival Curve

DISCUSSION

An important limiting factor in this study is the number of cases. Taking into account this limiting factor, we found some correlations in patients which need further documentation in larger series of patients. These correlations and our conclusions are:

1. There is no stastistically significant correlation between the number of cells transplanted and cellular recovery after BMT. (We also found this correlation in our thalassemic and aplastic anemia patients.)

2. Age, duration of disease, and CML phase as independent factors affecting outcome, were confirmed previously. Although we could not statistically confirm the effect of these factors on survival, our findings were in favour of this effect.

3. We found that the size of spleen may be related to disease recurrence; The larger spleen, the higher probability of CML recurrence. Cellular recovery was also found to be related to the size of spleen.

4. As is evident from previous reports, prior therapy with busulfan is associated with a greater risk of transplant-related mortality (Fisher: 0.06).

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