A Preliminary Report on the Feasibility of Outpatient Autologous Stem Cell Transplantation in Iran

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Abstract

Introduction: Autologous stem cells have greatly influenced the treatment of a variety of malignancies including Hodgkin/non-Hodgkins lymphoma and acute leukemias. This is a preliminary study comparing the time of engraftment, mortality rate and cost of treatment in outpatient versus inpatient autologous stem cell transplantation (SCT) in Iran.

Patients and Methods: 11 outpatients (6 Hodgkin Lymphoma (HL), 3 Non-Hodgkin Lymphoma (NHL) and 2 Acute Myeloid Leukemia (AML)) were compared with 32 inpatients (15 HL, 8 NHL and 9 AML) from May, 2008 to December, 2008. All patients were in complete remission and without significant organ failure. They received conditioning regimen (CEAM for NHL and HL, Busulfan and Etoposide for AML) and stem cell infusion in hospital. The day after SCT, the outpatient group was discharged and followed up by an outpatient SCT team to be re-hospitalized, if indicated.

Results: For outpatients and inpatients, the median period to WBC engraftment was 11 and 12 days (p-value=0.03), the timeframe to PLT engraftment was 15 and 25 days (p-value=0.20) and the number of transfused single-donor PLT was 3 and 4.5 units (p-value=0.21). The duration of neutropenic fever was 6 and 9 days (p-value=0.001), the duration of hospitalization after SCT was 0 and 16 (p-value<0.001), respectively. All outpatients are alive but three inpatients died between days +35 and +100 following SCT due to transplantation complications. The cost of the drugs used for treatment of neutropenic fever was 6 times higher in the inpatient group.

Conclusion: The outpatient autologous SCT in malignant hematological disorders is feasible and comparable to inpatient protocols in Iran.

Key words: Outpatient, Autologous Stem Cell Transplantation, Malignant Hematologic Disorders

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Introduction

With limited resources and competitive resource-allocation policies, justified measures have been taken to shorten the duration of hospital stay and costs of treatment.(1,2) In developed countries where patient follow-ups and outpatient care have established infrastructures, the domain of outpatient care has largely gone into the field of hematological malignancies(3,4). With the absence of such prerequisites, outpatient services might endanger the life of patients (especially in the field of hematological malignancies).

In addition, it is known that long hospital stays in the aplastic phase following high-dose chemotherapy with autologous stem cell support are expensive and increase the risk of hospital infection and pressure on the availability of beds. Investigations in these fields are scarce in developing countries.(5,1)

Keeping these issues in mind, our center has developed a local system for a home care regimen that allows patients to be at home for most of the aplastic period.

This preliminary investigation focuses on the feasibility of outpatient autologous stem cell transplantation in patients referred to the Shariati Hospital, Tehran, Iran.

Patients and methods

Between May, 2008 to December, 2008, six Hodgkin Lymphoma (HL), three Non- Hodgkin Lymphoma (NHL) and two Acute Myeloid Leukemia (AML) patients underwent outpatient SCT for their hematological malignancies.

The criteria for inclusion in this study was: acceptance of the patient, in a state of complete remission, age of the patient less than 45 years, a performance score of 80-100 or 0-2; normal heart, liver, kidneys and lung function. The distance from the patient's home to the hospital should be less than 60 minutes, the existence of an informed care giver available twenty-four hours a day, seven days a week, as well as acceptable living conditions at home and medical insurance.

The criteria that excluded patients were reluctance to becoming an outpatient, progressive or refractory disease and an age above 45 years.

Treatment protocol: All patients received high-dose chemotherapy (CEAM for NHL and HL, Busulfan and Etoposide for AML) and stem cell infusion in hospital. The day after stem cell infusion (day +1), patients were discharged (provided that they did not have fever or any other complication requiring treatment in the hospital).

Thereafter, an outpatient SCT team visited the patient once daily to check temperature, blood pressure, heart rate, presence of mucositis, oral intake, central venous catheter status and to administer intravenous (IV) medications. Blood samples were taken at home two times a week to check blood counts, chemical parameters and PBS.

Anti-infectious prophylaxis: Ciprofloxacin 500 mg/12 hours was orally (PO) administered until the patient recovered (neutrophil recovery or neutropenic fever). Fluconazole 150 mg/d PO until day +30 was administered. In cases of positive herpes simplex virus serology, acyclovir 400 mg/8 hours PO was administered until day +30. Patients treated at home received ceftriaxone 1 g/d IV from day +1 until the first day of febrile neutropenia or until first day of absolute neutrophil count higher than 1×10^9/l.

Other measures: Granulocyte colony stimulating factor (GCSF) 5 µg/kg/d IV from day +5 until neutrophil count reached at least 1×10^9/l for two consecutive days. RBC and platelet transfusions were administered when hemoglobin concentration and platelet count was below 8 g/dl and 10×10^9/l, respectively.

Patients were instructed to go to the hospital in the case of a temperature of 38°C or higher. After a chest x-ray and appropriate cultures, piperacillin and tazobactam (4.5 g/8 hours IV) was started. In the absence of hemodynamic instability, pneumonia, or cardiac or respiratory distress. Patients were discharged the same day to continue antibiotic IV treatment.

If WHO mucositis grade 3, signs of infection at the catheter insertion, or positive blood cultures taken from the indwelling IV catheter for coagulase-negative Staphylococci or if fever persisted more than 3 days, empirical vancomycin 15 mg/kg/q12h and amikacin 15 mg/kg/d IV was started in hospital. Amphotericin B 0.7 to 1 mg/kg/d IV was started if fever persisted more than 5 days.

Antibiotic treatment was maintained until the neutrophil count was superior to 1×10^9/l and patients were afebrile for at least 3 days with no infectious symptoms

Criteria for Re-hospitalization: Re-hospitalization was carried out in cases of fever persisting more than 3 days (despite treatment with tazocin), willingness of the patient or of the caregiver, uncontrolled nausea, vomiting or diarrhea; mucositis requiring total parenteral nutrition or IV morphics, hemodynamic instability, pneumonia, cardiac and/or respiratory distress.

Discharge criteria: Absolute neutrophil count should be higher than 1×10^9/l and remain afebrile without antibiotic administration for a minimum of 48 hours.

Granulocyte engraftment was defined as the first of 2 consecutive days with a neutrophil count of 0.5×10^9/l or higher, and platelet engraftment as the first of 2 consecutive days with an unsupported count of 20×10^9/l or higher. Febrile neutropenia was defined as a temperature of 38°C or higher in a patient with an absolute neutrophil count of less than 0.5×10^9/l.

Endpoints: Defined endpoints were: WBC/PLT recovery, transfusion of blood products, duration of neutropenic fever, duration, type and cost of antibiotics, duration of hospitalization and death.

Table 1. Comparison of age, gender and diseases between the two groups.

	Outpatient group (n=11)	Inpatient group (n=32)
Median Age (min-max)	**26 (16-41)**	**30 (16-45)**
Female/Male	**3/6**	**8/24**
HL	**6**	**15**
NHL	**3**	**8**
AML	**2**	**9**

HL: Hodghkin's Lymphoma, NHL: non-Hodghkin's Lymphoma, AML: Acute Myelogenous Leukemia.

Table 2. Comparison of measured variables between the two groups.

	Outpatient group (n=11)	Inpatient group (n=32)	P-value
Median hospital stay(after SCT)	0 (range:0-8)	16 (range:11-100)	<0.000
Median duration of neutropenic fever (day)	6	9	0.001
Median time for WBC recovery (day)	11	12	0.0261
Median time for PLT recovery (day)	15	25	0.2002
Median of transfused SD PLT(unit)	3	4.5	0.206
Median of transfused PC(unit)	0	0	0.048
Mean of antibiotic' s cost (Rls)	4,282,220	26,085,000	

SCT: Stem Cell Transplantation, WBC: White Blood Cell, PLT: Platelet, SD: Standard Deviation, PC: Packed Cell, Rls: Rials.

Results were compared with those observed in a control group of 32 patients individually matched to the group of patients treated inpatient for age,

Results

The median age of our outpatients was 26 years (16–41years). With respect to our outpatients, the median period of time to WBC engraftment was 11 days; the median period of time to PLT engraftment was 15 days; the median number of transfused single donor PLT was 3 units; the median duration of neutropenic fever was 6 days; the median hospital stay after SCT was 0 days (0-8 days). Only one patient needed to be re-hospitalized due to neutropenic fever (with no response to tazocin). No patient required packed cell transfusion and all patients are still living without any complication due to SCT. Table 1 and 2 compares the findings in two groups. Platelets and WBC recoveries are shown in figures 1 and 2.

All outpatients are still living. Four patients from other groups died between day +35 and +100 after SCT, due to transplantation complications. For the inpatient group, the cost of drugs, (just for neutropenic fever antibiotic therapy) was six times higher than for outpatients.

Discussion

Our preliminary study shows that outpatient management following SCT is safe in Iran. Our findings are comparable to all major studies in developed countries.(3,6,7,2) Outpatient management is shown to be better using most measurements compared to inpatients. Our preliminary analysis shows that, based on identical engraftment rates, a 0% mortality rate, programmed completion of the transplant procedure and better 35 and 100 day survival can be safely achieved on an outpatient basis.

Rehospitalization was required only for one patient; even though febrile neutropenia could easily be managed in an outpatient setting,(8) we did not take this risk regarding our patients because of newly-established protocol in our center. Clearly, this need could easily be met in the later stages of the instillation of our protocol.

Cost savings, which was found in our preliminary assessment, is being reported in studies done in other centers.(9,2,10) The importance of such findings must be emphasized for developing countries where these measures are just in their primary steps(5) It should be mentioned that a question of cost shifting(9) can be answered in a long range follow-up of patients which is beyond the scope of this study (but some studies have shown that there is no such phenomenon).(8) In addition, we have used only a totally outpatient management system(4) and a comparison with other outpatient SCT protocols is not possible.

The elimination of other hematological malignancies also reach a favorable outcome following outpatient SCT.(10,11) It should be remembered that successful outpatient management systems in all of the studies that have been done have used a well-established care-giving, the lack of which hinders any success in this process.(12)

A few studies in developing countries have shown improving results(5) with findings comparable to studies done in the best hematological centers of the world. It seems that even with the lack of a solid primary infrastructure, limited steps can be taken

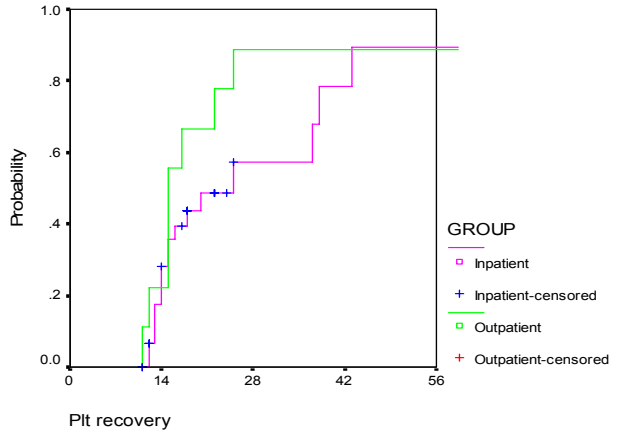

Figure 1. Platelets recovery.

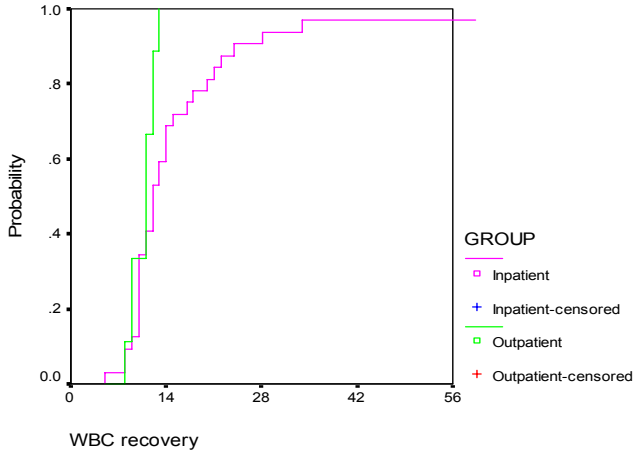

Figure 2. WBC recovery.

for an outpatient SCT in developing countries. The most important aspect of such findings would be for policy makers to consider outpatient systems as a measure of cost reduction in their overall policies.

Conclusion

With an appropriate patient selection and a sound care-giving system, outpatient ASCT is a feasible method that may improve the quality of life of patients which also reduces the costs of the procedure in Iran.

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