Allogeneic stem cell transplantation in acute myeloid leukemia

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Abstract

We report a case series of 12 patients with acute myeloid leukemia who underwent allogeneic stem cell transplant with a matched related donor. Male to female ratio was 1:1. The main complication post-transplant was graft-versus-host disease (n=7 patients). Transplant-related mortality involved one patient; cause of death was multi-organ failure. After a median follow up of 36.0±11.3 months, overall survival was 16%.

Introduction

Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow. This, together with the arrest of these cells, may result in hematopoietic insufficiency, such as granulocytopenia, thrombocytopenia or anemia. Since there is no cancer registry in Pakistan, a study carried out at our center in 2002 reported 74 adult patients with acute myeloid leukemia during an 8-year study period. Most younger patients with acute myeloid leukemia achieve complete remission with induction and consolidation chemotherapy regimens. However, these remissions are not sustainable even for patients who achieve complete remission 1 (CRI). The invariable risk of relapse requires consolidation with allogeneic stem cell transplant.

In developing countries, non-malignant diseases such as thalassemia major and aplastic anemia account for the largest number of transplant procedures; this is in complete contrast to the situation in developed countries. Here in Pakistan, treatment of AML is an expensive approach that is beyond the financial means of most of the population. This study ran from April 2004 till June 2012 and included patients with acute myeloid leukemia eligible for bone marrow transplant. Other inclusion criteria were: age up to 60 years, diagnosis of AML based on the French American British classification excluding acute promyelocytic leukemia, no history of myelodysplasia or previous cytotoxic therapy/radiation, and absence of concomitant disease.

Materials and Methods

This study ran from April 2004 till June 2012 and included patients with acute myeloid leukemia eligible for bone marrow transplant. Other inclusion criteria were: age up to 60 years, diagnosis of AML based on the French American British classification excluding acute promyelocytic leukemia, no history of myelodysplasia or previous cytotoxic therapy/radiation, and absence of concomitant disease.

Patients received induction chemotherapy with daunorubicin 45 mg/m² intravenously on Days 1-3 and cytarabine 100 mg/m² infusion on Days 1-7. Consolidation was given with high-dose cytarabine at a dose of 3 gm/m² administered by a 2-h infusion every 12 h on Days 1, 3 and 5. The most frequently used salvage cytogenetics. The invariable risk of relapse requires consolidation with allogeneic stem cell transplant (alloSCT) provided a survival advantage for an intermediate risk group. AlloSCT performed early in the disease course was not the optimal treatment for high-risk patients. Neither did it offer any advantage over intensive chemotherapy to low-risk patients. We report our experience of 12 patients with acute myeloid leukemia (relapsed and CRI) who underwent allogeneic stem cell transplant over a 7-year period. These results show the survival of patients from a developing country where stem cell transplant is an expensive approach that is beyond the financial means of most of the population.

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Key words: allogeneic transplant, acute myeloid leukemia, outcome.

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Results

From April 2004 till June 2012, 12 patients with acute myeloid leukemia received allogeneic stem cell transplant procedure. Male to female ratio was 1:1. Ten patients showed no cytogenetic abnormalities. One patient had Philadelphia positive acute myeloid leukemia while one had multiple abnormalities (Monosomy 8 and t11q; 23). Laboratory parameters of these patients are listed in Table 1.

Two patients received gender mismatched transplant while 3 had ABO blood group mismatched donors. All patients and donors were cytomegalovirus positive. Conditioning with busulfan and cyclophosphamide was given in 10 patients while the rest received total body irradiation based therapy. Median age was 26.5±11.5 years (range 9-50 years). One patient was under 15 years of age, while all the other patients were adults. Mean mononuclear cell count was 5.6×10⁹/kg (range 3.5-8.3×10⁹/kg). Stem cell source was peripheral blood progenitor cells for all patients. Engraftment was achieved in all except one patient. Median time to engraftment (absolute neutrophil count over 0.5×10⁹/L) was 26.3 days (range 20-39 days).

Post-transplant complications mainly included GVHD. Grade II acute GVHD was observed in 4 patients; chronic limited GVHD was seen in one patient and extensive GVHD in 2 patients, respectively. Biopsies were performed in n=4 patients for histopathological confirmation. Eight patients developed febrile neutropenia; of these, 2 had blood culture positive for staphylococcus species and enterooccus. Transplant-related mortality involved one patient; cause of death was multi-organ failure. After a median follow up of 36.0±11.3 months, overall survival is 16%. Causes of death include transplant-related mortality (n=1), relapse of disease (n=7), fulminant hepatic failure (n=1), and acute GVHD (n=1).

Discussion

Over the last decade, two important observations have been made with regard to treatment of acute myeloid leukemia: i) sustainable remission rates can be obtained with a combination of chemotherapy and allogeneic stem cell transplant; ii) cytogenetic abnormalities have been seen to be the most important predictor of outcome. 4,9

Here we have reported the outcome of 12 patients with AML who underwent allogeneic stem cell transplant. Due to the small size, firm conclusions cannot be made from this study.

There was no gender predilection observed although previous studies had reported an increased frequency in males. A study carried out in 2005 by Appelbaum et al.10 in 968 patients showed no change in gender ratio with age. AML is primarily seen in adults and, although in this study we stratified patients according to age for transplant eligibility, the overall median age for AML in this region is relatively low compared to that reported in the international literature. The median age in this study was 26.5 years; this is in line with a previous study carried out in our center in 2005. Similarly, another center in Pakistan has reported even lower age values, i.e. 21 years, when the authors evaluated the treatment outcome of de novo AML.11 Data reported in two studies from developed countries now show a median age of 52 and 67 years, respectively.12,13 The reason for this difference is difficult to ascertain; however, it may be a true ethnic or geographical variation as seen in the presentation of other diseases from our region.

Peripheral blood progenitor cells (PBSC) are now being used for almost all hematopoietic transplant procedures. These cells have higher numbers of CD34 and T lymphocytes.14 PBSC were used in all our patients. As a result, 11 of 12 patients engrafted. The only patient with graft failure died from multi-organ failure secondary to sepsis. Grade I acute GVHD is generally understood to be associated with an improved post-transplant outcome. Grades above this result in a worse overall survival since the beneficial effect of suppressing leukemia relapse is complicated by the morbidity and mortality associated with GVHD.15 Four patients in our study developed grade II acute GVHD. However, the cause of death in all these patients was disease relapse rather than the GVHD itself. In our group of patients, 3 underwent transplant procedure in CR1 (increased white blood cell counts, n=2; Philadelphia positive AML, n=1) whereas the remaining patients were in CR2. Small retrospective studies (less than 100 patients) have been reported for patients with AML not in remission undergoing stem cell transplant procedure. These studies have reported long-term survival rates of 20-30%.16 In 2000, Michallet et al.17 reported outcome of 379 patients. Of these, 230 received transplants with active disease. As expected, patients who underwent re-induction therapy first and achieved a complete remission did significantly better, with an overall survival of 32%. In 2010, the Center for International Blood and Bone Marrow Transplant Research reported the largest and most complete analysis of outcome of AML patients undergoing stem cell transplant.18 The study included more than 2000 patients and overall survival at three years was 19%. In our series, overall survival was 16%. Although our subset is small, the results are still comparable with the overall survival of AML in patients of developed countries.

Conclusions

Acute myeloid leukemia is not the most common indication for stem cell transplant. Median patient age at presentation in our study is relatively low compared to developed countries. There was no gender preference observed in our study. In Pakistan, the cost of stem cell transplant procedures is beyond the means of most of the population, and this means that they come to the attention of physicians late in the disease course. In spite of this, overall survival is still comparable to that reported in the international literature.

Table 1. Laboratory parameters of 12 patients with acute myeloid leukemia.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±standard deviation (range)</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.6±1.9 (7.8-12.8)</td>
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<tr>
<td>White blood cell count (×10⁹)</td>
<td>127.7±118 (18.2-292)</td>
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<tr>
<td>Platelets (×10⁹)</td>
<td>32±11 (19-45)</td>
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References

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