Pediatric Autologous Stem Cell Transplantation: A Comparison between Peripheral Blood Stem Cell and Bone Marrow

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Citation

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Abstract

Background: Ultra-high dose myeloablative therapy followed by autologous bone marrow transplantation has become an attractive therapeutic option for some pediatric cancer patients who do not achieve cure with conventional therapies. The source of these hemopoietic stem cells is either the bone marrow (BM) or the peripheral blood stem cells (PBSC). In this article, we review the various aspects of pediatric autologous stem cell transplantation and compare transplantation of stem cell collected from BM with that harvested from PBSC. Since most studies comparing PBSC and autologous bone marrow transplantation (ABMT) have found an engraftment advantage for PBSC, we also wanted to analyze if this translated into improved overall survival and disease free outcome.

Methods and Results: We analyzed the medical records of patients who underwent autologous bone marrow transplantation between March 1992 to July 2001 at Columbus Children's Hospital. They ranged from age's 1 year to 27 years (Median 5 years). The median survival time for 30 patients who underwent PBSC's transplant was 39.5 months, while for the 27 patients with ABMT transplant was 47.6 months. These transplantations were for a variety of disorders: neuroblastoma (n = 17), soft tissue sarcoma (n = 8). Ewing's sarcoma (n = 5), acute myelogenous leukemia (n = 4), non-Hodgkin's lymphoma (n = 3), Hodgkin's lymphoma (n = 2), Wilms tumor (n = 2), retinoblastoma (n = 2), desmoplastic small round cell tumor (n = 1), germ cell tumor (n = 1), and 12 cases of brain tumor, medulloblastoma (n = 7), ependymoma (n = 2), astrocytoma (n = 1), anaplastic glioma (n = 1), and glioblastoma multiforme (n = 1).

Patients were conditioned with a variety of preparative regimens. These regimens combined either one or more chemotherapy agents with total body irradiation (TBI), or cytotoxic drugs without TBI. All patients engrafted normally with an absolute neutrophil count (ANC) exceeding 500 X 106/L for three consecutive days. 12 of 30 patients who underwent PBSC transplant died compared to 12 of 27 who underwent ABMT. In both groups, relapse or progressive disease was the most common cause of death; ten cases each of PBSC and ABMT died from relapse or progressive disease. The other causes of death included: sepsis, multi-organ failure, cardiac toxicity, and post-treatment lymphoproliferative disorder. The median survival time until relapse or death for the PBSC's was 39.5 months compared to 47.6 months for ABMT. A log rank test comparing these two groups showed no statistical significance (log rank 0.013, P = 0.9).

Conclusions: Our study looking at the long-term advantage of PBSC over ABMT failed to show any benefit. There was no difference in the overall or progression free survival between the two groups.

INTRODUCTION

Children with advanced or recurrent malignancies have a poor prognosis. High dose chemotherapy followed by autologous hematopoietic rescue has improved this situation.($_1$) Thus, autologous stem cell transplantation has been introduced as consolidation for pediatric patients with high risk relapse tumors.($_2$) The most significant side effect of this high-dose chemotherapy is marrow ablation and thus this therapy must be accompanied by an infusion of hematopoietic stem cells. Then autologous stem cells could either be obtained from the marrow or the peripheral blood after mobilization with growth factors.

Since most studies comparing ABMT with PBSC have concentrated on their engraftment potential,([3,4,5]) in addition to studying various aspects of autologous transplantation, we wanted to study if there was a survival advantage of one group over the other.

METHODS AND RESULTS

PATIENT CHARACTERISTICS

57 children received high-dose chemotherapy followed by autologous stem cell transplantation between March 1992 and July 2001 at Columbus Children's Hospital. They ranged from 1 year to 27 years old (Median age 5 years). These transplantation's were for a variety of different diseases: neuroblastoma (n = 17), soft tissue sarcoma (n = 8), Ewing's sarcoma (n = 5), acute myelogenous leukemia (n = 4), non-Hodgkin's lymphoma (n = 3), Hodgkin's lymphoma (n = 2), Wilms tumor (n = 2), retinoblastoma (n = 2), desmoplastic small round cell tumor (n = 1), germ cell tumor (n = 1), and 12 cases of brain tumor, medulloblastoma (n = 7), ependymoma (n = 2), astrocytoma (n = 1), anaplastic glioma (n = 1), and glioblastoma multiforme (n = 1).

All patients were treated on protocols approved by the Institutional Review Board (IRB) at Columbus Children's Hospital.

STEM CELL HARVEST

The bone marrow was harvested under general anesthesia, and then filtered and cryopreserved in dimethyl sulfoxide (DMSO) in the standard fashion. The PBSC were mobilized with G-CSF (10-15 ug/kg/day S.C.) for four days before starting the collection. PBSC collections were carried out using a COBE spectra cell separator (COBE, Denver, CO, USA) through a double lumen apheresis catheter. In all cases of neuroblastoma, magnetic beads with monoclonal antibodies were applied for purging the stem cell. Similarly, 4-hydroperoxycyclophosphamide (4-HC) was used in AML. No purging was done in other cases.

CONDITIONING REGIMEN

Recipients were conditioned with a variety of preparative regimens (Table 1). These regimens combined either one or more chemotherapy agents with total body irradiation (TBI), or cytotoxic drugs without TBI. These included Children Cancer Group (CCG) protocols, limited and local institutional studies. The decision guiding selection of drugs was based on the predicted tumor-specific activity of these drugs. For most patients with neuroblastoma, the three drug combination, Melphalan (120 mg/m^2 – 180 mg/m^2 escalating dose with toxicity as limit), Etoposide (200 mg/m^2/day for 5 days), and carboplatin (500 mg/m^2 or area under the curve = 7 mg/ml x min via Calvert formula). For medulloblastoma, carboplatin 500mg/m^2 (or area under the curve = 7 mg/ml x min via Calvert) on days –8, -7, and –6; and thiotepa 300 mg/m^2 and etoposide 250 mg/m^2 on days –5, -4, and –3, followed by stem cell on Day 0. Patients with glioblastoma multiforme and astrocytoma received BCNU 100 mg/m^2 every 12 hours for a total of six doses, thiotepa 300 mg/m^2/day and etoposide 250 mg/m^2/day for 3 days.

Ewing sarcoma patients received TBI, Melphalan (120 mg/m^2 – 180 mg/m^2, escalating dose with toxicity as limit), with Etoposide (250 mg/m^2/day for 3 days). The Bu/Cy combination (Busulfan 16 mg/kg and cyclophosphamide 120 mg/kg) was used in AML, Etoposide (40 mg/kg) was added to the Bu/Cy combination in cases of both Hodgkin's and non-Hodgkin's lymphoma.

Relapsed or high-risk solid tumor patients were conditioned on thiotepa with an escalating dose of melphalan (local institutional protocol). Pre-transplant TBI of 10-12 Gy was given to 19 of 57 patients (14 with PBSC and 5 with ABMT).

SUPPORTIVE CARE

Indwelling central venous catheters were placed before conditioning. Patients were nursed in single rooms, ventilated with a HEPA system. All patients were given a low microbial diet without food sterilization procedures. Prophylactically, HSV positive patients received intravenous acyclovir, and orally nonabsorbable antibiotics (for selective intestinal decontamination) were given to all patients. Broad-spectrum antibiotics were administered if fever developed during aplasia. Amphotericin B was administered if fever persisted despite the initiative of empiric antibiotic therapy. Blood component therapy was used to maintain the hemoglobin level above 9 g/dl and platelets above 20X10^9/l; all cellular products were filtered, depleted of leukocytes, and routinely irradiated with 25 cGy.

ENGRAFTMENT

All 57 patients engrafted, which was defined as ANC>500/mm^3 for three consecutive days.

DISEASE STATUS PRE AND POST TRANSPLANT

As shown in Table 2, the majority of patients were in

complete remission prior to transplantation. Some, however, had refractory disease.

Except for four patients who never achieved complete remission post-transplantation, all others were free of their disease. Sixteen of these, however, relapsed and eventually died. The other causes of death included infection, multi-organ failure, cardiac toxicity, and post-transplant lymphoproliferative disorder (Table 3).

STATISTICAL ANALYSIS

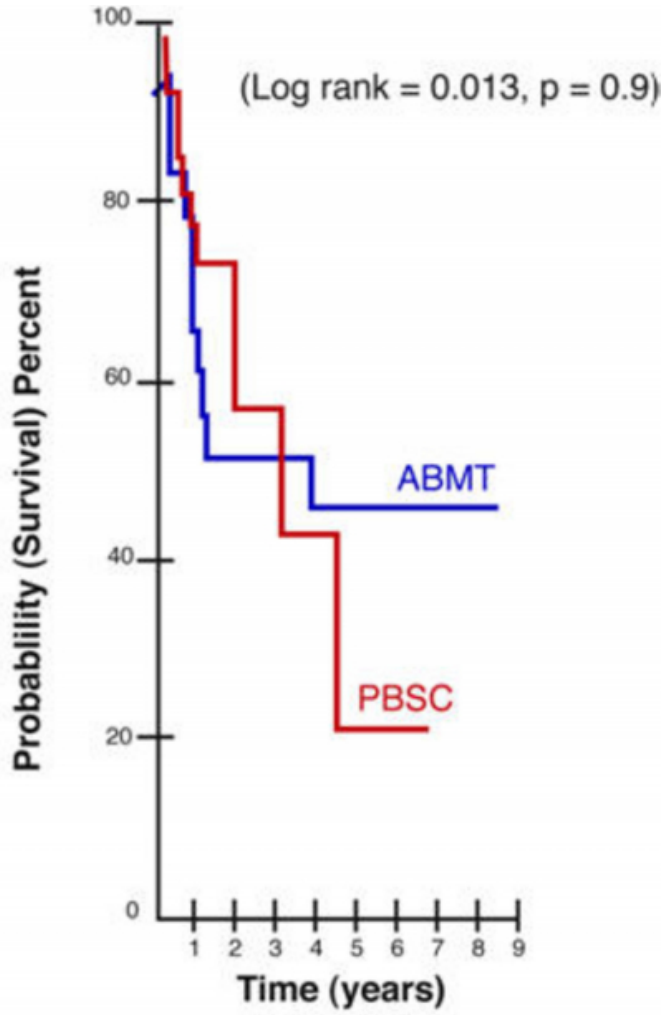
Kaplan-Meier curves were used to compute time to relapse or death. In each case, intervals were calculated from the date of transplantation until date of relapse/death, or date of last follow-up. Comparison between the two groups was done using the log-rank test.

COMPARISON OF SURVIVAL ANALYSIS BETWEEN THE TWO GROUPS:

12 of 30 patients who underwent PBSC died compared to 12 of 27 who underwent ABMT. The median survival time until relapse or death for the PBST was 39.5 months compared to 47.6 months for ABMT. A log rank test comparing these two groups showed no statistical significant difference between their survival (log rang 0.013, P = 0.9). Figure 1 shows the survival curves.

Figure 1

Figure 1



DISCUSSION

Most childhood cancers are chemosensitive.[6] However; children with metastatic disease generally have a poor prognosis despite an initially responsive disease. In addition, the prognosis of recurrent or refractory pediatric tumors is dismal, since patients are generally treated with intensive front line chemotherapy.[7] Alkylating agents, irradiation, anthracycline, vinca alkaloids and anti-metabolite all manifest steep dose-response curves against a variety of different tumor cell types.[8] Increased dose intensity is limited by both hematologic and non-hematologic toxicities. Therefore, mega-dose chemotherapy is followed by stem cell transplantation to overcome the hematologic toxicity.

We present our experience with 57 consecutive patients transplanted for a variety of different pediatric malignancies at Columbus Children's Hospital. These transplantation's were primarily in patients with solid tumors, however four

patients received autologous transplants for acute myelogenous leukemia (AML). Purging of stem cells were done in cases of neuroblastoma and AML. Magnetic beads with monoclonal antibodies was applied in cases of neuroblastoma, while 4-hydroperoxycyclophosphamide (4HC) was used in AML. We did not purge stem cells in other cases. To purge or not to purge? There is no conclusive evidence either way.([9,10,11,12]) The arguments in favor of purging include the reinfusion of tumor cells contributes to relapse, any therapy that reduces the tumor burden will promote better long-term survival and that purging does not affect engraftment. The arguments against purging include, there is no direct evidence that it causes relapse, the patient's immune system will eradicate any few re-infused tumor cells, and the procedure is costly.

The decision guiding which preparative regimen to use was based on the predicted tumor-specific activity of that regimen. For most patients with neuroblastoma the three drug combination of Melphalan, Etoposide and Carboplatin with TBI was used. (Table 3) Similarity for brain tumor patient's different preparative regimens were used. Except for one, all patients with medulloblastoma got carboplatin, etoposide and thiotepa. BCNU, Etoposide and thiotepa combination was used for glioblastoma multiforme and astrocytoma. Ewing's sarcoma patients were prepped with high doses of Etoposide (250 mg/m^2/day x 3 days) in combination with Melphalan and TBI.

The major reason for failure after transplantation for both PBST and ABTMT in our study was relapsed of the primary disease. The clinical significance of administering tumor contaminated stem cells contributing to relapse is unclear. From adult studies in patients with multiple myeloma, higher number of circulating tumor cells were associated with a shorter time to recurrence, but the presence of circulating tumor cells was not significant in a multivariate analysis that included plasma cell labeling index and B_2 microglobulin.([13]) The latter results suggest that the presence of circulating tumor cells was a sign of more aggressive disease rather than a direct cause of failure. Therefore, we fell future treatment protocols should focus on development of more effective multi-drug combination therapy.

CONCLUSION

PBSC are known for their hematopoiietic reconstitution advantage, easy technique of obtaining and reduced cost compared to ABMT, they however have a number of disadvantages. PBSC require cytokine (G-CSF or GM-CSF) use for colletion, and short-term pheresis catheter placement, under general anesthesia, with the attendant risk of pnemothorax, and infection. Our study was conducted to determine weather these characteristics translated into any long-term benefit. We found no difference in either tumor recurrence rate or overall survival between transplants done with either PBSC or ABMT. Therefore, within the limitations of our study, we conclude that either option of obtaining the stem cell can be chosen on the availability of a surgery room or a cell separator facility, and considering the patient characteristics and wishes.

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