ORIGINAL ARTICLE

Treating High Risk Childhood Solid Tumours with Autologous Peripheral Blood Stem Cell Transplantation - Early Experience in University Hospital, Kuala Lumpur

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Summary

Although survival rates for childhood cancers have improved steadily over the past two decades, the outcome for advanced stage solid tumours remains poor. Many of these tumours are chemosensitive but most chemotherapeutic regimens are limited by their haematological toxicities. Much attention is now focused on mega-dose chemotherapy followed by stem cell rescue in the treatment of disseminated neuroblastoma, rhabdomyosarcoma, germ cell tumour and brain tumours. There is a preferential shift towards peripheral blood stem cell transplantation instead of bone marrow transplantation because of its advantages of faster engraftment, decreased transfusion and antibiotic usage and shortened hospitalisation. This mode of therapy is dependent on technologies including peripheral blood stem cell harvesting, cell cryopreservation and thawing. These technologies were recently made available in Malaysia and we report our early experience.

Key Words: Childhood solid tumours, Peripheral blood stem cell, Transplantation

Introduction

Many childhood solid tumours like neuroblastoma, rhabdomyosarcoma, germ cell tumour and medulloblastoma are chemosensitive. However patients with these cancers often present with advanced disease and overall survival remains poor. Efficacy of cancer chemotherapy could be improved through dose escalation[1]. There is some evidence that intensification of chemotherapy improves clinical outcome[2]. This is also true for a number of adult tumours principally breast cancer[3,4] and lymphoma[5]. Increased dose intensity of chemotherapy is limited by both haematologic and non-haematologic toxicities. Most chemotherapeutic regimens now rely on haematopoietic stem/progenitor cell rescue to overcome the haematological toxicity. Sources of stem cells have included bone marrow, peripheral blood and placental cord blood. There is increasing evidence that peripheral blood stem cells (PBSC) engraft faster than bone marrow cells[6,7,8] thereby resulting in a decrease in hospital stay, use of transfusion products[9,10] and broad-spectrum antibiotics. The durability of engraftment with PBSC has also been proven[11,12]. There are conflicting reports on tumour contamination with PBSC compared with bone marrow cells[13,14] but the clinical significance of these tumour cells remain unclear. The preference for PBSC[15,16] has resulted in accumulation of a wide body of experience. However experience with paediatric patients remains relatively limited[17,18,19]. The difficulties of venous access, technical difficulties of PBSC collection in small children and fear

of exhaustion of the stem cell pool[17,20] are but a few of the challenges which face oncologists treating childhood cancers. We report our experience with the first two cases of peripheral blood stem cell transplantation (PBSCT) in University Hospital, Kuala Lumpur.

Case Reports

Case No.1

GJE aged 9 months presented with intractable vomiting. After investigations which excluded infections, a CT scan of the brain revealed a large cerebellar tumour. Near total resection of the tumour was performed and histopathological examination confirmed the diagnosis of medulloblastoma. In view of his young age and the general poor outcome of this disease, high-dose chemotherapy with stem cell rescue was attempted. The patient received chemotherapy consisting of cisplatinum, vincristine, cyclophosphamide and etoposide for five cycles together with granulocyte colony-stimulating-factor (G-CSF) support. After the first cycle of chemotherapy in December 1996, leukapheresis was performed to collect the patient's PBSC, making it the first time such a procedure was performed in Malaysia. A Medcomp Fr 7 haemodialysis catheter was inserted into his right jugular vein under general anaesthesia. Leukapheresis using the Fenwall CS3000 Plus blood cell separator (small chamber) was undertaken with red blood cell priming of the extra-corporeal line. Problems encountered during the leukapheresis included blood clots in the extra-corporeal line necessitating adjustment of the anticoagulant acid-citrate-dextrose (ACD-A). Another complication was infection around the exit site of the haemocatheter by *Staphylococcus epidermidis* progressing to bacteraemia even before the commencement of stem cell collection. Each leukapheresis procedure required 3 to 4 hours for completion. The patient had a total of 2 leukapheresis which ensured a good harvest of stem cells as measured by the number of CD34+ cells in the harvested product. The yield for the first and second harvests were 113.5×10^6 and 143.3×10^6 CD34+ cells respectively. The collected stem cells were cryopreserved without red cell depletion using 10% dimethyl sulfoxide (DMSO) and kept frozen in liquid nitrogen storage tanks.

Just prior to the PBSC transplantation, the patient was assessed by MRI brain scan and cytology of the cerebro-spinal fluid and found to be in remission for the disease. High dose chemotherapy consisting of carboplatinum, thiotepa and etoposide were used to condition him for the transplant. On the day of transplant, the cryopreserved stem cells were rapidly thawed in a 37°C waterbath and reinfused back to the patient. There were no untoward side effects seen. The patient's engraftment rate was extremely good with the absolute neutrophil count >500/µl by Day 7 and platelets >50,000/µl by Day 18. During the period of febrile neutropaenia, repeated blood cultures were negative. He was discharged home on Day 18. He remained well until Day 102 post-PBSCT when he developed a sudden left facial palsy. A CT scan of the brain confirmed the recurrence of tumour. The parents opted for no further intervention and the patient died of disease on Day 116 post-transplant.

Case No. 2

AYF aged 4 years presented with fever, progressive abdominal distension and weight loss. Physical examination revealed pallor with a large 11cm abdominal mass palpable below the right subcostal margin. A CT scan of the chest and abdomen confirmed the presence of a supra-renal mass extending through the hiatus of the diaphragm into the lower thoracic area and an associated right pleural effusion. A bone marrow examination showed involvement by small round blue cells. Urine vanillyl mandelic acid was positive. A diagnosis of Neuroblastoma Stage IV was made and the patient was started on chemotherapy consisting of alternating cycles of adriamycin, cyclophosphamide, vincristine, dacarbazine with cisplatinum, cyclophosphamide and teniposide. The patient defaulted from treatment after 4 cycles of chemotherapy only to reappear 7 months later in an emaciated ill state with an even larger abdominal mass, right haemothorax and gross bone marrow involvement. She was restarted on chemotherapy using a different regime. After 5 cycles of chemotherapy, her bone marrow was free of disease. PBSC collection was performed via a haemocatheter (Medcomp 7 Fr) inserted in the right subclavian vein during the recovery phase of chemotherapy with

augmentation by G-CSF. A total of 2 leukapheresis were performed with CD34+ cell yields of 2.8 x 10^6 and 24.6 x 10^6 each. No complications were encountered during the PBSC harvests. The stem cells were cryopreserved with 10% DMSO and kept in liquid nitrogen.

Following PBSC collection, the patient underwent a laparotomy for resection of the primary thoraco-abdominal neuroblastoma. As the tumour had infiltrated the intercostal and paravertebral muscles, only gross total resection could be achieved. Irradiation was given to the thoracic area with macroscopic residual disease. She was then prepared for her PBSCT with conditioning using carboplatin, teniposide and melphalan. On the day of transplant, her stem cells were thawed and reinfused with no complications. The patient's absolute neutrophil count was >500/µl by Day 13 while her platelet count was >50,000/µl on Day 49. She was discharged well on Day 91 post-transplant and is currently well with no evidence of disease.

Discussion

Stem cell transplantation for the treatment of malignant and non-malignant disorders gained acceptance in the 1970s. Today there is no doubt that stem cell transplantation for acute lymphoblastic leukaemia in 2nd remission, acute myeloid leukaemia and chronic myeloid leukaemia offers better survival rates compared with conventional chemotherapy[21,22,23,24]. Increasing numbers of children with congenital immune deficiences and metabolic disorders are benefiting from transplantation. Although the role of stem cell transplantation in childhood solid tumours is not clearly established, there is an increasing trend towards this modality of treatment particularly for disseminated neuroblastoma, rhabdomyosarcoma and germ cell tumours, together with high-risk brain tumours.

The initial source of stem cells was the bone marrow either autologous (from the patient) or allogeneic (from a healthy donor). Studies showed that progenitor stem cells were also present in peripheral blood and numerous strategies were tested to mobilize and increase the number of these progenitors for collection[25,26,27,28,29]. The combination of chemotherapy- recovery with G-CSF has proven to be one of the most effective mobilization techniques and was employed for both the cases described. The number of stem cells which can be mobilised varies between patients and is low for patients who are heavily pre-treated with multiple courses of chemotherapy. This is reflected in the stem cell yields in Case No. 2.

Successful collection of stem cells from peripheral blood for transplantation is a culmination of various technologies which had matured over the 1980s. These technologies included improved blood cell separators and apheresis procedures, blood cell component isolation and cryopreservation. In addition immunophenotyping techniques using the surface marker CD34 for identification of the stem cell were also developed for rapid and reproducible results. The refinement of these various technologies made available PBSC for haematopoietic rescue after high dose chemotherapy. Moving in tandem, clinicians were formulating more intensive chemotherapeutic regimes in their efforts to improve cure rates for advanced cancers which remained chemosensitive.

In University Hospital, Kuala Lumpur, allogeneic bone marrow transplantation had been performed for paediatric patients since April 1987. It was only in August 1996 that we were able to start cryopreservation initially for placental cord blood samples and later in December 1996 for PBSC. We are still at an early stage of the learning curve. To date we have conducted 34 PBSC collections on 13 children with a median age of 4.5 years (range 5 months - 17 years) and weight of 13.1kg (range 5.7 - 53 kg). The training of apheresis nurses and medical laboratory technologists present another challenge. Immunophenotyping techniques identifying CD34+ cells need standardization. Cell culture to test the viability and proliferative capabilities of stem cells, is routinely performed in established transplant centres and may need to be established here.

We see the potential for PBSC transplantation following high dose chemotherapy for advanced cancers in childhood. Speedier engraftment translates into shortened hospitalisation with decreased transfusion and antibiotic support and would be advantageous in this age of cost consciousness. This has proved true even with the limited number of PBSCTs we have performed. Both our patients engrafted on Day 7 and 13

respectively which compares favourably with the median day of engraftment of Day 20 for our patients with bone marrow transplantation[30]. Collection of PBSC from very small children presents problems with venous access but these are not insurmountable. Use of radial arterial lines[17], silastic central venous catheters[31,32], polyurethrane haemocatheters[18,19], polyurethrane central venous catheters[32] has all been described for paediatric patients with variable success. We find that the polyurethrane haemocatheter allows a good blood flow but requires a general anaesthetic for insertion in the paediatric population. Although infection of the haemocatheters has seldom been reported, we find this an extremely common problem in our hands.

Conclusion

Our limited experience demonstrates the feasibility of PBSC collection for cryopreservation and transplantation after high dose chemotherapy in small paediatric patients and its immediate advantages are already evident. These advantages are particularly critical in Malaysia where transplant resources are limited and waiting lists are long. Indeed PBSCT is expected to supplant BMT both in the autologous and allogeneic setting. Whether this strategy will translate into improved survival and disease free outcome for our patients with advanced cancers awaits larger studies with longer follow up.

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