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Specificities of Autologous Haematopoietic Stem Cell Transplantation in Children: A Single Centre Experience

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Abstract

Background: Autologous haematopoietic stem cell transplantation (AHSCT) is now an integral part of the treatment of high-risk solid tumours in children. However, specific characteristics and problems related to paediatric patients must be taken into account. Considering these tumours are rare, indications, efficacy and practical issues of autologous transplantation have been a topic of research and discussion.

Results: We analysed 46 children with high-risk solid tumours and lymphomas, with a median age of 5.4 years who underwent AHSCT without tumour cell purging. Median follow-up of patients after AHSCT was 37.5 months. There were no lethal outcomes due to high-dose chemotherapy toxicity or transplantation-related consequences. 11 patients (23.9%) died while 35 (76.1%) out of 46 patients survived. Overall five-year survival of all transplanted patients was 73%. There was a significant difference in the survival of neuroblastoma patients compared to the remainder of solid tumour patients (82% vs. 38%, log-rank test X^2=6.86, P<0.01). Unlike lymphoma and neuroblastoma patients, the worst survival rates were amongst patients with brain tumours and rhabdomyosarcoma. Patients in complete remission before the transplantation had more favourable survival rates than patients who had achieved partial remission (log-rank test X^2=16.37, P<0.01).

Conclusion: Our results confirm success of AHSCT in children with neuroblastoma and lymphomas in extending their survival. For other tumour patients and patients in partial remission before the transplantation, survival may be increased by introducing double AHSCT with post-transplant immunomodulatory therapy.

Keywords Autologous haematopoietic stem cell transplantation; Children; Solid tumours

Introduction

High-dose chemotherapy (HDC) with autologous haematopoietic stem cell transplantation (AHSCT) is becoming a preferred treatment of unfavourable high-risk solid tumours in children. Malignant tumours that require AHSCT treatment are considered rare. These can be lymphomas or solid tumours such as neuroblastomas, Ewing's sarcomas/primitive neuroectodermal tumours (PNET), rhabdomyosarcomas, nephroblastomas, brain tumours and germ-cell tumours [1-4].

There is a high correlation between chemotherapy dose increase and favourable treatment response in most childhood tumours. Increase of chemotherapy doses within the myeloablative values can overcome tumour's therapy resistance and achieve desired clinical improvement [1].

Indications for stem cell transplantation include disseminated high-risk tumours or tumours with an expected short survival using conventional treatment (expected long-term survival < 30%). AHSCT is also indicated in cases of partial response to induction therapy and disease relapse [1,2].

Here we present the results of patients who were treated for solid malignant tumours and lymphomas with high-dose chemotherapy and autologous haematopoietic stem cell transplantation as well as specific issues and solutions encountered in every-day practice of a paediatric centre for AHSCT.

Materials and Methods

Patients

We analysed a total of 46 children with high-risk solid tumours and lymphomas who were treated with high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation at the Department of Haematology and Oncology, Children's Hospital Zagreb between December 2005 and December 2012. Patients with different high-risk solid tumours who had achieved a complete remission or partial remission with no progressive disease were eligible for AHSCT. Most patients who received AHSCT were suffering from high-risk neuroblastoma (meeting the criteria of either metastatic disease, age > 1 year or MYCN amplification in any age). All patients suffered from a tumour disease that was either metastatic at diagnosis or had relapsed following therapy. These patients were required to have normal kidney and liver function, left ventricular ejection

fraction >50%, and their Lansky's performance status >70% before AHSCT.

A summary of the patients' demographic and clinical data is presented in Table 1. Clinical and laboratory data were consensually retrieved from patient charts in Children's Hospital Zagreb and from the database of the Department of Transfusion Medicine and Transplantation Biology, University Hospital Centre Zagreb, Croatia.

Number of patients	46
All	26
Neuroblastoma	5
Brain tumors	4
Rhabdomyosarcoma	1
Nephroblastoma	5
Lymphoma	5
Ewing sarcoma / PNET	
Male/female	27/19
Age median (years)	5.4
Age range (years)	0.417.3
Body weight median (kg)	18.4
Body weight range (kg)	Aug78
Time from diagnosis to transplantation (months)	Aug40
Time to engraftment median (days)	11
Time to engraftment range (days)	21Oct
Disease status before transplantation (PR/CR)	17/29
Followup median (months)	37.5
Followup range (months)	Apr96
Deceased/survived	Nov35
All	22Apr
Neuroblastoma	2Mar
Brain tumors	2Feb
Rhabdomyosarcoma	Jan00
Nephroblastoma	0/5
Lymphoma	4Jan
Ewing sarcoma / PNET	
Survived after AHSCT	35
CP	7
CR	28

Table 1: Patient characteristics PR: Partial Remission; CR: Complete Remission; AHSCT: Autologous Haematopoietic Stem Cell Transplantation; CP: Cancer Present (Residual Disease Or Relapse)

Peripheral blood stem cell collection

A cycle of chemotherapy or cyclophosphamide (2 g/m^2/day over 2 days) was used as chemotherapy-induced mobilisation. It was followed by administration of granulocyte colony-stimulating factor (G-CSF, 5-10 μg/kg/day). Haematopoietic stem cells were harvested mostly after 4 chemotherapy cycles from peripheral blood using leukapheresis in all patients. Our goal was to collect 5×10^6 CD34+ cells per kilogram of body weight. However, we considered CD34+ cell count of 2×10^6/kg to be minimally acceptable for a viable transplant. After monitoring for adequate CD34+ cell number in peripheral blood, peripheral blood stem cell (PBSC) collection was started using cell separator (COBE Spectra: Version 6.0. Terumo BCT, Lakewood, USA). In small children (weight ≤ 15 kg) cell separator was primed with leukodepleted and irradiated red cells to prevent haemodynamic complications and dilution anaemia. Large volume leukapheresis (four blood volumes for each patient per procedure) was performed in all children, and the combination of acid-citrate-dextrose (ACD) and heparin was used as anticoagulants. Citrate-induced hypocalcaemia in infants was avoided with calcium infusions during apheresis [5,6]. The transplant was finally processed, without tumour cell purging, and stored frozen in liquid nitrogen [7]. We found one transplant to be inadmissible due to low viability of stem cells and one stem cell collection was unsuccessful due to low CD34+ cell count.

Treatment

Ensuing detailed clinical and laboratory examinations, which excluded any active infections, we proceeded with high-dose chemotherapy. HDC was defined by the appropriate treatment protocol according to the diagnosis (NB2004, EuroEwing 99, HIT 2000, NHL-BFM 2004). All patients received a single high-dose chemotherapy. Cytostatic agents that were used in high-dose therapy for certain types of tumor can be found in Table 2.

Tumour type	Highdosage chemotherapy
Neuroblastoma	melphalan, etoposide, carboplatin
Ewing's sarcoma	busulfan, melphalan
Brain tumours	thiotepa, carboplatin, etoposide
Nephroblastoma	melphalan, carboplatin, etoposide
NonHodgkin lymphoma	busulfan, etoposide, cyclophosphamide
Hodgkin lymphoma	carmustine, etoposide, cytarabine, melphalan
Rhabdomyosarcoma	melphalan, etoposide, carboplatin

Table 2: Cytostatic agents used in the highdose therapy, depending on type of tumour.

HDC was followed by reinfusion of autologous PBSC. Appropriate premedication regimen was initiated in all patients, to prevent complications during or after the reinfusion process. The

premedication regimen included paracetamol, diphenhydramine, hydrocortisone and diazepam. Time to neutrophil engraftment was measured from transplant to the first of two consecutive days with an ANC > 0.5×10^9/L. Time to platelet engraftment was measured from the time of transplant to the time of patient's independence to platelet transfusions (the recommended transfusion trigger point for platelets was 20×10^9/L or less).

Statistical analysis

Standard parametric techniques were used to describe the patients' demographic and clinical characteristics. Overall survival (OS) was defined as the interval between the time of AHSCT and patient's death. Univariate analysis of OS was performed as outlined by Kaplan and Meier with the corresponding 95% confidence intervals (CIs). The comparisons of survival curves were made by log-rank test. Statistical analysis was performed using MedCalc version 10.4 computer program.

Results

Patient characteristics

From December 2005 until December 2012, we have treated 46 patients with high-dose chemotherapy and autologous haematopoietic stem cell transplantation in our hospital. There were 19 female and 27 male patients with a median age of 5.4 years (range: 0.4-17.3 years) and median body weight of 18.4 kg (range: 8-78 kg) (Table 1). The most common indication for AHSCT in our patient group was high-risk neuroblastoma. The number of transplanted patients sorted by type of tumour in our group can be seen in Table 1.

Treatment

Following the mobilisation and collection protocol, all HSC transplants were evaluated according to the CD34+ cell number. Median yield of CD34+ cells was 11.54×10^6/kg per patient. Median number of leukapheresis performed was 1 per patient (range: 1-4 leukaphereses). The targeted dose of 5×10^6/kg CD34+ cells was realised in 91% of patients. Red cell priming of cell separator in small children and prevention of citrate-induced hypocalcaemia ensured that there were no serious complications during the leukapheresis procedure. However, two infant patients presented with a perforated vein upon femoral catheter insertion, which required replacement of the catheter and consequent administration of blood products to manage bleeding.

Reinfusion of autologous stem cells followed HDC according to the appropriate protocol. The reinfusion process had no serious complications following premedication regimen. Most common complications were nausea and vomiting, while temporary hypertension or tachycardia were seldom exhibited. Patients with a fever during aplasia were treated according to our hospital's empirical guidelines, which include piperacillin/tazobactam as the first line of treatment, and meropenem with vancomycin as the second line of treatment. Severe systemic fungal infections were avoided with early administration of lipid or liposomal complex amphotericin B preparations. Strong side-effects to lipid complex amphotericin B (fever, shivering) necessitated the use of caspofungin in three patients. One neuroblastoma patient, who had one kidney, exhibited a transient increase of creatinine levels. Most patients presented with a moderate mucositis and diarrhoea. Only one patient developed a severe haemorrhagic diarrhoea (Clostridium difficile negative). The most severe complication occurred in a 2-year-old female neuroblastoma patient who presented with a reversible hyperammonaemia and short-term coma (lasting for 17 hours). This condition was accompanied with a sudden increase in body weight and hepatomegaly without elevated liver function tests or bilirubin levels.

Outcome

There were no lethal outcomes due to high-dose chemotherapy toxicity or transplantation-related consequences. All patients achieved engraftment. The median time to neutrophil engraftment was 11 days (range: 10-21). The median time to platelet engraftment was 26 days (range: 22-30 days). Median follow-up of patients (after AHSCT) was 37.5 months (range: 4-96 months). 11 patients (23.9%) died while 35 (76.1%), out of 46 patients survived. Overall five-year survival of all transplanted patients was around 73% (Figure 1). There was a significant difference in overall five-year survival of neuroblastoma patients compared to the remainder of solid tumour patients (82% vs. 38%, log-rank test X2=6.86, P<0.01) (Figure 2). Unlike lymphoma and neuroblastoma patients, the worst survival was amongst patients with brain tumours and rhabdomyosarcoma as seen in Table 1.

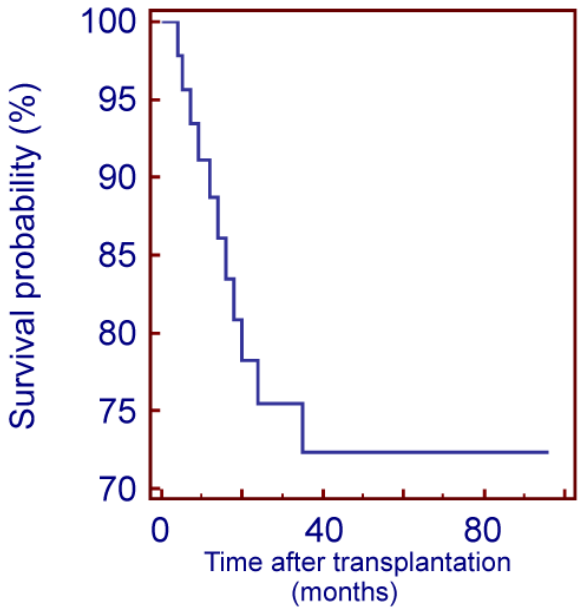

Figure 1: Kaplan-Meier survival curve showing survival probability of all transplanted patients in Children's Hospital Zagreb. Fiveyear overall survival is 73%.

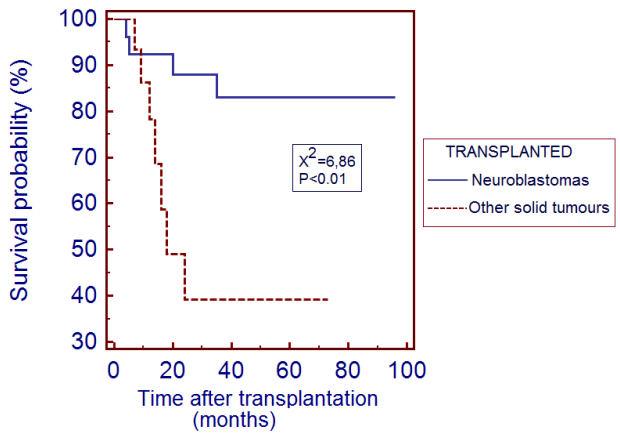

Figure 2: Kaplan-Meier survival curve of transplanted patient. The relationship of neuroblastoma and the other solid tumour patients, excluding lymphoma patients (logrank test X^2=6.86, P< 0.01, 95% CI=1.183316.2009).

28 out of 35 surviving transplanted patients were in complete remission until the end of the follow-up, while 7 patients in that group had relapsed or still had residual tumour disease (Table 1).

Patients in complete remission before the transplantation had significantly more favourable survival rates than patients who had achieved partial remission (log-rank test X^2=16.37, P< 0.01) (Figure 3).

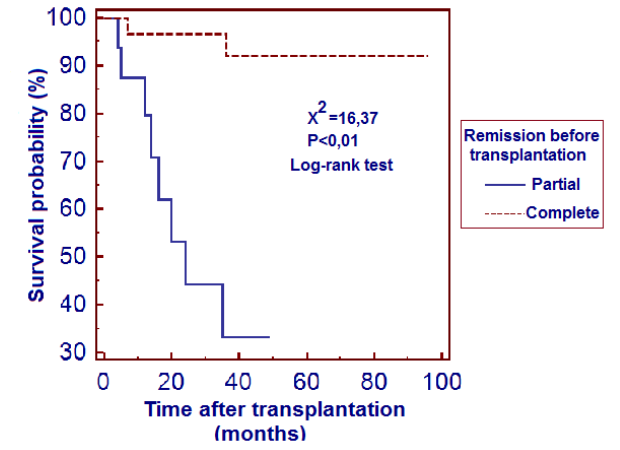

Figure 3: Kaplan-Meier survival curves of transplanted patients, depending on the state of remission before transplantation. There is a significant difference in survival demonstrated by the logrank test (X^2=16.37, P< 0.01, 95% CI=2.847149.4568).

Discussion

In children with solid tumours the results of autologous haematopoietic stem cell transplantation are generally equal or better than the conventional treatment. In our study we observed promising results in lymphoma and neuroblastoma patients, contrary to patients suffering from brain tumours and sarcoma.

Our results support that neuroblastoma is the most common paediatric solid tumour, the treatment of which includes autologous stem cell transplantation. AHSCT is the prinicipal part of multimodal therapy of high-risk neuroblastoma patients [1,2,8,9]. High-dose chemotherapy usually consists of melphalan, etoposide and carboplatin [8]. High-risk patients (metastatic disease, age > 1 year, MYCN amplification) have survival rate of 10-15% if they had not received AHSCT. With AHSCT, the disease-free survival of these patients rises to 30-50% [8,9].

In our centre, Ewing's sarcoma/PNET is the second most common indication for autologous transplantation in treating patients suffering from solid tumours. Conventional chemotherapy can achieve 3-5 year disease-free survival in around 20% of patients with large tumours with lung metastases. These survival rates can decrease to approximately 5% if these patients develop early relapse and/or multifocal bone disease [1]. High-dose chemotherapy in Ewing's sarcoma consists mostly of melphalan and bulsulfan. Utilising AHSCT in the treatment of these patients accomplishes equal or higher survival rates with 3-5 year disease-free survival in 20-65% of patients [10-15]. Our experiences confirm that high-risk Ewing's sarcoma/PNET patients certainly belong to the group that can greatly benefit from stem cell transplant.

However, disease outcome of patients suffering from brain tumours in our study did not change significantly after HDC/AHSCT. This could in part be explained with the well-known problem of blood-brain barrier. Compared to "high-grade" gliomas and ependymomas, AHSCT is known to achieve better results in recurrent, refractory or high-risk medulloblastomas, primitive neuroectodermal tumours of the brain, atypical teratoid rhaboid tumours and germinomas of the central nervous system with disease-free survival of 10-50% [16-18]. Nevertheless, dose-dependant therapeutic response of tumours of neuroectodermal origin that was previously reported in these studies did not manifest in our results [2,19-21]. We also observed poor results in rhabdomyosarcoma patients. However, in other studies with a larger number of patients, outcome of soft-tissue sarcoma patients after HDC/AHSCT does seem a little more promising. Patients with rhabdomyosarcoma bear disease-free survival of 30-40% after HDC/AHSCT [3,22]. Better results have usually been observed in tumours sensitive to chemotherapeutics and in patients who were in remission before the transplantation [19]. In the group of patients suffering from brain tumours or rhabdmyosarcoma, we cannot make firm conclusions due to low number of treated patients in our study.

Our results confirm success of AHSCT in children with neuroblastoma and lymphomas in the extending their survival. For other tumour patients, and patients in partial remission before the transplantation, survival may be increased by introducing double AHSCT with post-transplant immunomodulatory therapy [23-27].

However, it has to be noted that our study was retrospective and non-randomised, with a small number of heterogeneous patients, making our result insufficient for conclusive evidence. These problems together with the issues of different transplant characteristics and non-standardised means of conditioning also limit most other analyses in evaluating effectiveness of AHSCT [2].

When examining procedures and practices of autologous haematopoietic stem cell transplantation special care should be taken to address potential problems with this procedure in child patient. We

often find antecubital intravenous access to be insufficient. This issue is usually circumvented using large bore double lumen central venous catheters for apherisis. Broviac catheters are not preferred for this use as their lumen may collapse under negative pressure. In infant patients femoral catheters are preferred. However, these bear risks of vein occlusion, erosion and perforation of the vein and bleeding. Femoral catheters also carry a larger risk of infection. In small children, where small circulating volume is used, the cytapherisis machines are required to fill up the remainder of the relatively large extracorporeal volume with concentrated erythrocytes. This method prevents the occurrence of haemodynamic complications and dilution anaemia. Standard ACD anticoagulant can cause symptomatic hypocalcaemia in children. This side effect can be avoided with the combination of ACD and heparin together with calcium infusions during apheresis [6].

We employed peripheral blood stem cells (PBSC) as autologous transplants due to certain advantages they bear in comparison to stem cells harvested from bone marrow. Those are shorter periods of neutropaenia and thrombocytopaenia, decreased risk of tumour contamination, shorter hospital stays and smaller treatment costs. These benefits resulted in peripheral haematopoietic stem cells becoming the mainstay of autologous transplant even in patients with neuroblastoma, whose average age is below 3 years old [28].

In our decision not to purge the transplants from tumour cells, we have considered several aspects of the process. Yaniv et al. have proven that CD34- purging might not be as reliable due to a certain number of residual tumour cells in peripheral blood expressing CD34+ [29]. But despite studies proving residual tumour cells in PBSC transplants, a large multi-centric randomised COG study compared survival of transplanted neuroblastoma patients in relation to tumour cell purging. The results indicated that purging PBSC transplants does not significantly impact survival. The reason to this was considered to be either incomplete purging or residual tumour in the patient. These findings suggest that non-purged peripheral blood stem cell transplants are acceptable to support myeloablative therapy in high-risk neuroblastoma patients [30,31]. Tumour cell purging also significantly increases the price of the procedure, which further questions its necessity. We have therefore established a practice that includes 4 cycles of chemotherapy preceding PBSC collection, in hope to achieve sufficient in vivo purging of tumour cells in peripheral blood.

These experiences encountered in our centre indicate that AHSCT in children carries certain specificities. We believe proper management of these particularities of AHSCT in paediatric patients are crucial for good results. Familiarity with the subject and specialised knowledge were key to our results being comparable to those of other studies.

In conclusion, autologous haematopoietic stem cells transplantation is not only highly indicated in the treatment of patients with high-risk recurrent lymphomas, but also as consolidation of a multimodal treatment of patients with metastatic neuroblastoma. AHSCT also gives promise of improved survival rates in certain groups of other high-risk solid tumours (Ewing's sarcoma/PNET, rhabdomyosarcomas, brain tumours). Nonetheless, disease relapse remains the main cause of unsuccessful transplantation in all patients [2]. Double high-dose chemotherapy with double (tandem) autologous transplantation is becoming more widely used in recent years. However, prospective randomised trials are required to evaluate efficacy of multiple transplants compared to a single transplant [23]. Another problem in improving the success of AHSCT is treatment of minimal residual disease. We believe a promising avenue for minimal residual disease treatment after AHSCT might lie in the use of immunomodulatory therapeutics [24-27].

Regardless of the challenges it faces, HDC with AHSCT remains an efficient treatment option that will, with further improvements, indubitably contribute to increasing favourable outcomes in children suffering from solid high-risk tumours and lymphomas.

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