·Original Article in English·

Effect of autologous peripheral blood stem cell transplantation on advanced malignant solid tumors in children

Dong-Sheng HUANG, Suo-Qin TANG, Li-Zhen LIU, Jian-Wen WANG, Ying LIU, Jie-Yan WANG, Shan-Gen LÜ

Department of Pediatrics, Chinese PLA General Hospital, Beijing 100853

Abstract: Objective The advanced solid tumor in children is not responsive to regular chemotherapy. This paper aims at studying the feasibility and effect of high dose chemotherapy combined with autologous peripheral stem cell transplantation (APBSCT) in the treatment of high risk advanced solid tumors in children. **Methods** Thirteen patients, including 7 cases of malignant lymphoma and 6 cases of neuroblastoma, were given APBSCT after receiving complete remission (CR) or partial remission (PC). The median disease duration before transplantation was 10 months. Before transplantation, 12 patients had CR and 1 had PR. Mobilization of stem cells was performed with chemotherapy plus G-CSF or GM-CSF in 11 and chemotherapy alone in 2 patients. The collecting mean number of MNCs, $CD34^+$ cell and CFU-GM was (6.85 ±2.65) $\times 10^8$/kg, (15.82 ±12.93) $\times 10^6$/kg and 17.87 ±17.94 colons/10^4 cell respectively. The conditioning regimen consisted of cyclophosphamide plus TBI as basic program in 6 patients, melphalan plus etoposide, carboplatin in 5 patients and busulfan plus melphalan in 2 patients. **Results** The median times of the amount of WBC being more than 0.5 $\times 10^9$/L and 1.0 $\times 10^9$/L and of thrombocytopenia being more than 20 $\times 10^9$/L were 12, 15 and 19 days respectively. A follow-up of 48 months (ranging from 1 month to 144 months) showed that survival and death rates after transplantation were 77% (10/13) and 23% (3/13) respectively. No death due to the transplantation was found. **Conclusion** APBSCT can significantly improve the prognosis of patients with advanced solid tumors.

[Chin J Contemp Pediatr, 2004, 6(1): 11-14]

Key words: Solid tumor; Autologous Hematopoietic stem cell transplantation; Child

自体外周血造血干细胞移植在小儿恶性晚期实体肿瘤的临床应用

黄东生,唐锁勤,刘立真,王建文,刘英,王杰燕,吕善根 解放军总医院小儿内科,北京 100853

[**摘　要**] **目的**　小儿晚期实体肿瘤对常规化疗效果欠佳,该文探讨大剂量化疗并自体外周血干细胞移植(APBSCT)治疗小儿高危晚期实体瘤的可行性及疗效。**方法**　13 例恶性实体肿瘤患儿(恶性淋巴瘤 7 例、神经母细胞瘤 6 例),在其完全缓解(12 例),部分缓解(1 例)后进行了 APBSCT 治疗。移植时病程中位时间 10 月。11 例用化疗加重组人粒-单细胞集落刺激因子(rhGM-CSF)或重组人粒细胞集落刺激因子(rhG-CSF)动员,2 例采用常规化疗方案作为动员剂。所采集单个核细胞(MNC)为(6.85 ±2.65) $\times 10^8$/kg。$CD34^+$ 细胞为(15.82 ±12.93) $\times 10^6$/kg。CFU-GM 集落为(17.87 ±17.94)个/10^4 细胞。预处理方案中 6 例基本方案为全身放疗加环磷酰胺。7 例未用 TBI,仅以马法兰为主做为预处理方案(马法兰 + 卡铂 + 足叶乙甙 5 例,白消胺 + 马法兰 2 例)。**结果**　移植后白细胞 > 0.5 $\times 10^9$/L、> 1.0 $\times 10^9$/L、血小板 > 20 $\times 10^9$/L 的中位时间分别为 12 天、15 天、19 天。中位随访时间 48 月(1 月～144 月)。至今总生存率 77%(10/13),死亡率 23%(3/13),无移植相关死亡。**结论**　APBSCT 是治疗小儿晚期实体肿瘤,明显改善其预后的重要治疗方法。　[**中国当代儿科杂志,2004, 6(1): 11-14**]

[**关　键　词**] 实体肿瘤;自体造血干细胞移植;儿童

[**中图分类号**] R73　[**文献标识码**] A　[**文章编号**] 1008-8830(2004)01-0011-04

[Received] September 30, 2003; [Revised] November 25, 2003

[Biography] Dong-Sheng HUANG(1963-), Male, Master, Associate Professor, Specializing in childhood hematology/oncology.

[Correspondence Author] Dong-Sheng HUANG, Department of Pediatrics, Chinese PLA General Hospital, Beijing 100853, China (Email: dongshenghuang 2002 @hotmail.com).

Malignant solid tumours, especially neuroblastoma (NB), are common in children and account for 7 % - 14 % of childhood malignant tumors, just only less than leukemia and lymphoma. Furthermore, they are serious and not responsive to regular chemotherapy. Although high dosage chemotheropy will completely or partially remit NB, they are still inclined to relapse unless further powerful treatment is carried out. So experts in this field have come to an agreement that intensive chemotherapy with APBSCT treatment can obviously improve the survival rate according to the sensitive tumour's dosage effecacy principle. Thirteen children with advanced malignant solid tumor hospitalized in the Chinese PLA General Hospital received the treatment of autologous peripheral blood stem cell transplantation (APBSCT) from March, 1991 to July, 2003. Below is a summary of the stem cells' harvest time, the harvested cells' amount, the re-infused cells' amount, the bone marrow reconstruction time, disease free survival (DFS) period after transplantation and transplant-related complications.

Subjects and methods

Subjects

Thirteen children (9 males and 4 females) ranging from 4 to 9 years old (average age of 6.85 years and weighing 16 - 35 kg were enrolled in this study. Seven of these cases were diagnosed as malignant lymphoma(ML), including 1 case of Hodgkin disease IV phase in complete remission (CR_1), 4 cases of non-Hodgkin lymphoma III phase in CR_1 and 2 cases of non-Hodgkin lymphoma IV phase in CR_1, and 6 cases were diagnosed as NB, including 3 cases in CR_1 at III phase and 3 in partial remission (PR_1) at IV phase. The ML children had received regular chemotherapy alone and the NB patients had been treated with chemotherapy, operation and partial radiotherapy before transplantation. Their bone marrows had no tumor infiltration or had been in CR. Transplantation took place when the patients had a CR or PR for more than 6 months. The disease course before transplantation went through between 6 months to 26 months (median duration of 10 months). The patients were performed with regular follow-up instead of chemotherapy after transplantation.

Harvesting, freezing of stem cells and transplanting of APBSC

The patients were treated by two methods. The 2 cases before 1992 were performed with regular chemotherapy alone and the remaining 11 cases received chemotherapy with recombination human granulocyte colony-stimulating factor (rhG-CSF) or recombination human granulocyte mono colony-stimulating factor (rhGM-CSF). The mobilization projects included: (1) cytoxan (CTX) + vincristine (VCR) + daunorubicin (DNR) + prednisone (Pred); (2) VCR + DNR + Pred + etoposide (VP-16); (3) CTX + DNR + VCR; (4) cisplatin + VP-16 etc. The 11 patients began to receive subcutaneous injections of rhG-CSF or rhGM-CSF when the amount of leucocyte dropped to below 2×10^9/L. They were stopped one day before the harvest of APBSCT. The dosage of rhG-CSF or rhGM-CSF was 5.8 ± 0.7 μg/kg every day. The harvest started when all the patients' leucocyte recovered to over $1.5 - 3.0 \times 10^9$/L and was done every morning at the blood transfusion department until the mononuclear cells (MNC) were totally above 5×10^8/kg. The type of cell separator machine initially used was a V30 but it was then replaced by a CS-3000plus and a COBE spectra4. Most cases just needed 2 or 3 times but one case needed to be harvested 6 times. The harvested cells were frozen and preserved at an environment of - 196 ℃. They can be rapidly thawed in a 40 ℃ waterbath and then be re-infused into the patients' bodies through veins[1].

Conditioning regime

The basic treatment program for 6 cases was total body radiotherapy (TBI) plus CTX. The TBI dosage was 6.5 - 8.0 Gy (average 7.45 Gy) given by twice and the dosage rate reached to or was less than 5 cGy/min. The administered drugs included: 6 cases with CTX 50 mg/kg for two days; and 1 case with Ara-C 1 - 2 g/m^2 for two days; 5 cases with VP-16 100 - 300 mg/m^2 for 2 - 3 days; 3 cases with DNR 20 - 40 mg/m^2 for two days; 1 case with idarubicin 10 mg/m^2 for two days; 1 case with carboplat

(CBP) 150 mg/m^2 for two days; and 1 cases with mitoxantrone 15 mg/m^2 for two days. The other 7 cases were pre-treated with melphalan instead of TBI and the programs were (1) 5 cases with melphalan 70 mg/m^2 for 3 days plus CBP 425 mg/m^2 for 2 days plus VP-16 338 mg/m^2 for 2 days; (2) 2 cases with busulfan 30 mg/m^2 for 3 days plus melphalan 150 mg/m^2 for 1 day. The medicines were administered once daily except busulfan which was given once every 6 hours. Three cases were additionally administered with the broad spectrum cell protectant, amifostine (0.4 g), 30 minutes before chemotherapy or radiotherapy.

Results

The amount of stem cells harvested and transplanted

After the mobilization of stem cells, the number of peripheral white blood cells (WBC) dropped to the lowest level [(1.25 ±0.85) ×10^9/L] within 6.45 days. When WBC level rose to (5.83 ±3.55) ×10^9/L, the harvesting began and the average number of harvests was 3.28 times in succession. The amount of gathered MNC was (6.85 ±2.65) ×10^8/kg. The flow cytometer assayed that the quantity of CD34$^+$ cells was (15.82 ±12.93) ×10^6/kg. After cultivation, the quantity of CFU-GM was 17.87 ±17.94 clones/10^4 cells. The amount of transplanted MNC was (4.85 ±2.74) ×10^8/kg.

Blood-building function recovery

The amount of peripheral WBC dropped to zero after +4.00 ±2.52 days and blood platelet dropped to the lowest level [(23.42 ±10.88) ×10^9/L] after +7.25 ±4.11 days. The median durations of WBC level being more than 0.5 ×10^9/L and more than 1.0 ×10^9/L and blood platelet amount being more than 20 ×10^9/L were +12, +15 and +19 days respectively. The patients were discharged from the laminar flow room after 28.2 ±11.5 days.

Outcome after therapy

The median follow-up time was 48 months (ranging from 1 month to 144 months) until July of 2003 including one case whose follow-up time was more than 10 years, 3 cases of more than 5 years, 3 cases of more than 2 years and 3 cases of more than 1 year. Three cases died at 2 months, 4 months and 8 months after transplantation respectively. One of them was a NB case which died of cerebral hemorrhage due to slow platelet recovery after transplantation. The other two with ML died of cerebral infarction and DIC because of bone marrow relapse and the amount of WBC in one case was as high as 630 ×10^9/L. The mortality was 23% (3/13) and no one died during the earlier period of transplantation (period staying in laminar flow room).

Related transplantation complications

There were 7 cases of fever during transplantation (53.85%), and most were caused by perianal and upper respiratory tract infection; 6 cases of buccal cavity ulcer (46.15%); 5 cases of liver functional lesion (38.46%); 5 cases of hypokalemia (38.46%); 2 cases of convulsion(one was induced by melphalan, the other was by amifostine; 1 case of biliary tract infection and 1 case of hematuria. The long-term complications after transplantation included 1 case of hepatitis C after blood transfusion (earlier-period case) and 1 case of cataract. No transplant-related death occured.

Discussion

It is common knowledge that high dose chemotherapy is accompanied by high risk. Based on the authors' data, the method of high dose chemotherapy plus APBSCT may be safer and more reliable for treating sensitive solid tumors. Weaver et al[1] have also reported that it was more efficient than traditional chemotherapy and that the mortality related with APBSCT among 1 000 cases registered in the tumor office was below 3%. The mortality in this study was zero, which agreed the above conclusion.

In this study, some children were administered with higher dosage of melphalan, CBP, etc. than that reported[2], but the serious erosion of buccal cavity and digestive tract did not occur because of the reasonable hydration, basification, administration of some protective medicines and careful nursing. It showed that the children with solid tumors could endure high dosages of chemotherapeutic drugs in the pretreatment.

Amifostine is the first kind of broad spectrum cell protectant. It does not protect the cells of tumors but those of normal tissue selectively from the damage of chemotherapy or radiotherapy, and it will not reduce the effect of chemotherapy or radiotherapy[3]. In this study there were three cases administered with amifostine and none of them had serious erosion of buccal cavities and digestive tracts. Two of them had a rapid recovery of leucocyte mount, and so the duration of hospitalization and medical cost were reduced. One of them had hands numbness possibly caused by the hypocalcemia associating with amifostine.

There were two IV phase lymphoma cases in this study whose bone marrow relapsed rapidly after transplantation even though they were in CR before transplantation. The amount of WBC in one case was as high as 630×10^9/L and the patient died of cerebral infarction and DIC. The possible reason of bone marrow relapse was that after transplantation the immune function was low and this caused the escaping tumor cells or the tumor cells mixed in the return-transplanted stem cells to grow quickly.

Untill now the median follow-up time for survival cases was 48 months. One case was more than 10 years, three cases were more than 5 years, three cases were more than 2 years and three cases were more than 1 year. The mortality was 23% (3/13). There was no deaths during the earlier period after transplantation and this proved that APBSCT was a very important therapeutic option which could significantly improve the prognosis of patients with malignant solid tumors. Recently the patients with NB were administrated with retinoic acid for induced therapy and a composite therapy of IL-2, interferon, etc. after transplantation. The purpose was to improve the survival rate and decrease the relapse after transplantation.

The method of APBSCT used in this study was appropriate for those advanced malignant solid tumours which were sensitive to chemotherapy or radiotheropy, such as ML and NB but it needed to be carried out at the appropriate time. The patients must be treated with 5 - 6 chemotherapy courses before transplantation and have CR or PR during transplantation. Moreover the heart, lung, liver, kidney and haematogenous functions must work normally. The NB patients must be treated with chemotherapy, operation and local radiation and have CR or PR before transplantation.

[References]

[1] Weaver CH, Schwartzberg LS, Hainsworth J, Greco FA, Li W, Buckner CD, et al. Treatment related mortality in 1000 consecutive patients receiving high dose chemotherapy and peripheral blood progenitor cell transplantation in community cancer centers [J]. Bone Marrow Transplant, 1997, 19(7): 671 - 678.

[2] Demirer T, Ilhan O, Mandel NM, Arat M, Gunel N, Celebi H, et al. A phase I dose escalation study of high-dose thiotepa, melphalan and carboplatin (TMCb) followed by autologous peripheral blood stem cell transplantation (PBSCT) in patients with solid tumors and hematologic malignancies [J]. Bone Marrow Transplant, 2000, 25(7): 697 - 703.

[3] Renner S, Krumpelmann S, Bruchelt G, Wiesinger H, Niethammer D, Klingebiel T. Effect of amifostine on neuroblastoma during high dose chemotherapy: in vivo and in vitro investigations [J]. Anticancer Res, 2000, 20(6B): 4531 - 4538.

(Edited by Min XIE)