APPLICATION OF TANDEM PBSC TRANSPLANTATION IN CHILDREN NEUROBLASTOMA TREATMENT

Klymnyuk G.I., Pavlyk S.V., Shayda O.V., Khranovska N.M., Skachkova O.V.

National institute of cancer, Pediatric department, Kyiv, Ukraine

Summary. Despite significant advances made over the past several decades in the treatment of malignant solid tumors in children, the results of treatment of patients with high-risk neuroblastoma are few satisfactory. Purpose. Consider the possibility, safety and features of tandem high-dose chemotherapy in the treatment of children with high-risk neuroblastoma. From 2012 to intensify treatment, we used double (tandem) high-dose chemotherapy in 9 patients. The first element tandem chemotherapy was busulfan and melphalan. CPCS transfusion was performed at a dose of 2.9 - 4.3 h106 SD34 + cells per kilogram of patient. The second element of transplantation was topotecan and cyclophosphamide. CPCS transfusion was performed at a dose of 3.0 - 7.0 h106 SD34 + cells per kilogram of body weight. The second element was carried out at intervals of 2.1 months (1.8 - 3.0 months). The first element of chemotherapy, patients underwent satisfactorily. Febrile neutropenia was observed in 5 of 9. Leukocytic engraftment reached at 9 - 12 days, platelet - 12 - 34 days. In a second element chemotherapy in one patient was observed neurotoxicity. Febrile neutropenia was observed in 3 of 9 patients. Leukocytic engraftment reached at 9 - 11 days, platelet - at 12 - 22 days. Holding dual (tandem) high-dose chemotherapy with autologous transplantation for the treatment of neuroblastoma CPCS children possible. Toxicity two stage tandem transplantation was higher proportionate to the dose received drugs, but not greater than expected.

Key words: solid tumors in children, neuroblastoma, high-dose chemotherapy, stem cells of peripheral blood, tandem transplantation

Introduction. In spite of significant success achieved during several past decades in malignant solid tumors treatment in children the treatment outcomes in patients with high risk neuroblastoma still remain poorly satisfactory. At application of traditional complex treatment (chemotherapy, surgical intervention, high-dose chemotherapy

with autologous haemopoietic stem cells transplantation, radiotherapy, differentiation therapy) that was practiced in many study protocols generations, according to different authors data, it was possible to achieve the survival rate from 25% to 40%. Considering that neuroblastoma refers to chemo-sensitive tumors and also has a number of genetically specified biological features, such results make scientists from many countries to look for new treatment methods or to modify already existing methods. As one of the methods for improvement of complex therapy can be referred introduction of mIBG (I-131 metaiodobenzylguanidine) therapy into first-line therapy [1], antibodies, and different types of vaccines application as supportive therapy [2]. Application of double high-dose chemotherapy with haemopoietic stem cells (HSC) transplantation also deserves attention [3-7].

Currently there were only several pilot trials available for this procedure application. In this way, according to the results of Chicago Pilot II Study that examined patients' group of 26 persons from August 1995 till January 2000 at average follow-up period of 38 months from the moment of diagnosing, the recurrence free survival rate was 57% [3]. Dana Farber Cancer Institute and Children's Hospital (Boston), Children's Hospital (Philadelphia), Emory Children's Centre (Atlanta) and Primary Children's Medical Centre (Utah) from 1999 till 2000 jointly examined 97 patients with diagnosis: "high risk" neuroblastoma, and 82 patients from them received tandem transplantation of PBSC. Total survival rate at follow-up of 3, 5, and 7 years was, respectively, 74%, 64%, 54%. Average follow-up period was 5.3 years [4].

Aim of work. To determine efficiency of tandem high-dose chemotherapy in treatment of children with high risk neuroblastoma.

Materials and methods of study. High-dose chemotherapy with autologous peripheral blood stem cells (PBSC) transplantation in complex high risk neuroblastomas treatment in the Department of Children's Oncology of the National Cancer Institute is applied from 2007. In 2012 application of double (tandem) high-dose chemotherapy as intensification method for consolidation treatment stage was started. During the mentioned period tandem transplantation was performed in 9

patients. All patients were children aged from 2 to 13 years with neuroblastoma of high risk group. In three patients tandem transplantation was provided as consolidation for neuroblastoma early local recurrence, on the background of pronounced clinical effect (mass dimensions reduction according to CT data), after 4 courses of second-line therapy (topotecan, doxorubicin, vincristine). In other patients tandem transplantation was prepared and provided as first line therapy, because initially patients referred to high risk group (disseminated process, N-myc antigen amplification). Autologous PBSC collection was provided after combined stimulation (cytostatic + colony-stimulating factor) with apparatus Frezenius AS 104, AS TEC 204.

First element of tandem high-dose chemotherapy for all patients was identical and standard: oral busulphan 16 mg/kg (days -6; -5; -4; and -3), and intravenous melphalan 140 mg/m^2 (day -2). As preparation for high-dose chemotherapy bowel decontamination with antibacterial, antiviral, antifungal remedies, also seizures and pneumocystosis infection prophylaxis were provided. PBSC transfusion was performed at day "0" by intravenous infusion of freshly thawed leucoconcentrate in amount of 2.9 – 4.3x10^6 CD34+ cells per kilogram of patient's weight. Autologous PBSC transfusion that was performed after pre-medication with antihistamine preparations and corticosteroids application proceeded without complications.

Second tandem transplantation element was regimen on topotecan basis applied in all patients: intravenous topotecan 2.0 mg/m^2/day (day -8; -7; -6; -5), and intravenous cyclophosphamide 60 mg/kg/day (day -5; -4; -3). PBSC transfusion was performed at day "0" by intravenous infusion of freshly thawed leucoconcentrate in amount of 3.0–7.0x10^6 CD34+ cells per kilogram of patient's weight. Second element was performed in 2.1 months interval (1.8–3.0 months).

Study results. First element of high-dose chemotherapy was satisfactory tolerated by all the patients. 4-th degree leucopenia and 4-th degree thrombocytopenia were observed in all patients. Febrile neutropenia was seen in 5 of 9 patients and it lasted from 1 to 7 days. Leucocytic engraftment was achieved at day +9 - +12, thrombocytic engraftment – at day +12 - +34.

At second element of high dose chemotherapy (CT) in one patient, neurotoxicity in the form of periodic short-term clonicotonic seizures was recorded. Chemotherapy was discontinued early (she received 2/3 of cyclophosphamide dose and full topotecan dose). After retrospective analysis of anamnesis data and chart review it was determined that in this patient on the background of chemotherapy short-term episodes of disorientation and aggressive behavior were registered – for this reason she was consulted by neurologist and received prescribed sedative therapy. Other patients satisfactory tolerated high-dose chemotherapy. Leucopenia, 4-th degree thrombocytopenia, and oral mucositises of different intensities were observed in all patients. Febrile neutropenia was seen in 3 of 9 patients and it lasted also from 1 to 7 days. Leucocytic engraftment was achieved at day +9 - +11, thrombocytic – at day +12 - +22.

Reliable difference in duration of leucocytic and thrombocytic blood stem renewal after first and second element of high-dose chemotherapy was not detected. Somewhat more frequently we had to use blood components transfusion (platelets concentrate and erythrocyte concentrate) after the second element.

Ad interim one patient died from disease progression. Two patients receive treatment for recurrence that developed after tandem transplantation, other patients without signs of recurrence continue treatment (scheduled radiation therapy, surgical intervention, differentiation therapy).

Conclusions. Provision of double (tandem) high-dose chemotherapy with autologous PBSC transplantation in children with neuroblastoma is achievable. Chemotherapy regimens toxicity is proportionate to the received preparations doses. Efficiency of treatment provided should be measured by further exploration of this issue.

Table. Toxicity and features supporting high-dose chemotherapy treatment courses

	PBSC transfusion, (x10/6/kg)		duration of leucopenia IV / Leucocytic engraftment, (d)		duration of thrombocytopenia IV, / thrombocytic engraftment, (d)		Febrile neutropenia, (d)		transfusion of platelets concentrate		transfusion of erythrocyte concentrate	
	I	II	I	II	I	II	I	II	I	II	I	II
1	3,6	4,5	6/11	5/9	5/16	0/12	-	-	0	0	0	0
2	3,6	7,0	7/11	10/9	21/29	16/22	1	-	2	3	1	2
3	3,3	3,0	8/12	11/11	28/34	16/19	-	1	7	5	0	1
4	14,0	14,0	8/12	11/10	11/14	19/20	1	7	2	5	1	2
5	10,0	10,0	5/10	10/10	4/12	20/20	1	-	0	3	1	2
6	3,0	3,1	9/9	10/9	13/15	17/17	-	-	4	3	0	0
7	2,9	3,4	6/10	11/10	11/16	18/19	6	7	2	5	0	1
8	3,8	4,0	7/11	11/10	6/13	13/13	1	0	1	3	1	3
9	4,3	4,6	8/11	9/11	6/13	15/18	-	4	2	5	1	3

References

1. Joseph H. Antin (2009) Manual of Stem Cell and Bone Marrow Transplantation. Cambridge University Press. : 188.
2. Philip Lanzkowsky (2011) Manual of pediatric hematology and oncology. 5th ed. Hardbound : 1058.
3. Kletzel M., Katzenstein H.M., Haut P.R. et al. (2002) Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: results of the Chicago pilot II study. J. Clin. Oncology, 20(9): 2284–2292.
4. George R.E., Li Sh., Medeiros-Nancarrow Ch. et al. (2006) High-risk Neuroblastoma Treated With Tandem Autologous Peripheral-Blood Stem Cell-Supported Transplantation: Long-Term Survival Update. J. Clin. Oncology, 24(18): 2891–2896.
5. Qayed M., Chiang K.Y., Ricketts R. et al. (2012) Tandem Stem Cell Rescue as Consolidation Therapy for High-Risk Neuroblastoma. Pediatr Blood Cancer, 58(3): 448–452.
6. Granger M., Grupp S.A., Kletzel M. et al. (2012) Feasibility of a tandem autologous peripheral stem cell transplant regimen for high risk neuroblastoma in a cooperative group setting: a Pediatric Oncology Group study: a report from the Children's Oncology Group. Pediatr Blood Cancer, 59(5): 902–907.
7. Sung K.W., Son M.H., Lee S.H. et al. (2013) Tandem high-dose chemotherapy and autologous stem cell transplantation in patient with high-risk Neuroblastoma: Results of SMC NB-2004 study. Bone Marrow Transplantation, 48: 68–73.