

# Transplantation for ultra high-risk neuroblastoma patients: effect of tandem autologous stem cell transplantation

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**Cite this article as:** Yılmaz E, Samur MB, Özcan A, Ünal E, Karakükcü M. Transplantation for ultra high-risk neuroblastoma patients: effect of tandem autologous stem cell transplantation. J Health Sci Med 2021; 4(6): 943-948.

## ABSTRACT

**Aim:** Neuroblastoma is a tumor with a high mortality rate originating from primitive sympathetic ganglion cells. In recent years, the definition of "ultra high-risk" has been used, in which the response to treatment is added in addition to the disease characteristics. In this study, the results of tandem high-dose Iodine 131 (<sup>131</sup>I) metaiodobenzylguanidine (MIBG) and tandem autologous hematopoietic stem cell transplantation (HSCT) in patients who were diagnosed as refractory after first-line treatments and considered with ultra-high risk nöroblastom (NBL) in Erciyes University Medical Faculty Pediatric Bone Marrow Transplant Center were shared.

**Material and Method:** Eleven patients who underwent tandem MIBG and autologous HSCT with the diagnosis of refractory/ultra high-risk NBL between 2011 and 2021 were included in the study. Patient's data were obtained retrospectively using an electronic or manuscript medical record.

**Results:** Tandem autologous HSCT and MIBG treatment were applied to 11 patients with a median age of 40.5 months who were diagnosed with refractory/ultra high-risk neuroblastoma. In our study, the overall survival rate was 54.5% and event-free survival (EFS) was 39% at a median follow-up of 20.7 (7.8-105.6) months. Of the 6 surviving patients, 4 are followed in complete remission and 2 in partial remission.

**Conclusion:** Our study is the only study that includes a group of patients who received tandem high-dose MIBG and tandem autologous HSCT transplantation in refractory NBL patients without cytokine and immunotherapy. Tandem transplantation and MIBG therapy in ultra-high-risk NBL cases remain promising with acceptable toxicity. Adding immunotherapy to this treatment protocol and combining it with new treatment modalities such as anaplastic lymphoma kinase (ALK), which also takes into account genetic characteristics, may increase survival and event-free survival rates.

**Keywords:** Neuroblastoma, tandem stem cell transplantation, children, tandem MIBG

## INTRODUCTION

The spectrum of neuroblastic tumors (this term includes neuroblastomas, ganglioneuroblastomas, and ganglioneuromas) is one of the most common lethal malign diseases that arise from primitive sympathetic ganglion cells (1). Neuroblastoma (NBL) is the most common extracranial malignancy overall in the first year of life as the cause of 15% mortality of childhood cancers and disease is characterized by a heterogeneous group of histopathologic appearance, biologic characteristics with onset usually before age 5 years old (2-4). Neuroblastomas constitute 13% of childhood cancers in Turkey (5). Remarkably divergent courses of tumors are typically associated with patient age, tumor stage, and histology, genetic and chromosomal abnormalities (6). Global

surveys estimate the occurrence of NBL in the range of eight to ten per million children 0-14 years (2,3).

NBL remains distinct from other solid tumors. The disease has ranged from extremely aggressive metastatic disease to spontaneous regression forms, this is probably due to their unique histological and biological character (6). While the most adrenal gland involvement was observed (40%), up to 25% followed by abdominal, 15% thoracic, 10% other nervous sympathetic systems; location of the tumor determines the symptoms including abdominal mass or pain, weakness, constipation and bladder dysfunction, palpable non-tender subcutaneous nodules, anemia, and bone pain. Elevated levels of catecholamines

may lead to significant morbidity and death but also "atypical" presentation such as horner syndrome, proptosis, periorbital ecchymoses, or opsoclonus myoclonus syndrome expected (1,2,6). Previous studies have shown that the most robust prognostic factors are age, stage, metastasis, histology, Stage of the tumor at the time of diagnosis, and amplification of the N-Myc oncogene (7). Markers associated with a poor prognosis include ferritin, lactate dehydrogenase (LDH), and neuron-specific enolase (NSE). However, these markers have become less important due to the discovery of N-Myc amplification, deletion of chromosome 1, and heterozygosity at 11q23 (1,7).

Standard care of high-risk NBL is defined as multi-modal treatment which includes induction chemotherapy, surgical tumor resection, immunotherapy, consolidative high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT), post-consolidation therapy to treat minimal residual disease including isotretinoin, post-transplant radiotherapy (8,9,10). Detection of GD2 and ALK expression in neuroblastoma cells brings up alternative treatment options (11). Survival is around less than %15 before these intense therapies but, it is still below 50% despite all these treatment regimens (9,10). The use of high-dose chemotherapy with autologous HSCT rescue and Iodine 131 (<sup>131</sup>I) metaiodobenzylguanidine (MIBG) has still insufficient in survival however, patients with the high-risk disease requires treatment with multi-modal therapy (3). Especially, refractory and ultra high-risk patients (which including treatment response) have an extremely poor prognosis; despite gradual improvements chemotherapy, surgery, radiotherapy, and HSCT with %10-15 survival (8,12).

Studies over the past few years show that survival of NBL patients undergoing tandem transplantation is significantly better, by the time tandem HSCTs are getting the standard first-line therapy in The United States of America step by step (8,13,14). There are still institutes that apply myeloablative regimens consolidated with immunotherapy and isotretinoin as standard therapy (15). Thus, improvement of treatment strategies of stem cells is warranted.

In this study, the results of tandem high-dose MIBG and tandem autologous HSCT in patients who were diagnosed as refractory after first-line treatments and considered with ultra-high risk NBL in Erciyes University Medical Faculty Pediatric Bone Marrow Transplant Center were shared. In comparison to previously published bone marrow transplantation experience, our data is the only study with both tandem high-dose MIBG and tandem autologous HSCT transplantation for pediatric ultra high-risk neuroblastoma patients.

## MATERIAL AND METHOD

### Patients

Eleven patients who underwent tandem MIBG and autologous HSCT with the diagnosis of refractory/ultra high-risk neuroblastoma at Erciyes University Pediatrics Bone Marrow Transplant Center between January 2011 and January 2021 were included in the study. Patient's data were obtained retrospectively using an electronic or manuscript medical record.

The study was carried out with the permission of Erciyes University Faculty of Medicine Clinical Researchs Ethics Committee (Date: 08.07.2020, Decision No: 2020/371). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Diagnosis, Risk Classification, Genetic Study

All patients were diagnosed with tissue biopsy. Molecular analyzes were performed on tissue samples taken at the time of diagnosis at Dokuz Eylül University Oncology Institute. Bone marrow aspiration and biopsy were used for staging the disease, MIBG, positron emission tomography/computed tomography (PET CT) and/or whole-body magnetic resonance imaging (MRI) were used as imaging modalities. In the evaluation of patients' response to treatment, biochemical parameters such as lactate dehydrogenase, ferritin, NSE; if there is bone marrow involvement at the time of diagnosis or if additional symptoms developed, bone marrow aspiration and biopsy; MIBG, PET CT and/or MRI were used as imaging modalities. The patients were staged according to the International Neuroblastoma Staging System (INSS) (16). The patients' response to treatment was evaluated using the international neuroblastoma response criteria (17).

### Treatment Protocols

All patients received the Turkish Pediatrics Oncology Group Neuroblastoma 2009 (TPOG 2009) treatment protocol. Tumor resection was performed before and/or after the protocol according to the size, localization and invasion of the tumor. Interim evaluation was made after the 3<sup>rd</sup> or 4<sup>th</sup> cycle. Following the interim evaluation, hematopoietic stem cells were collected from the patient with the help of an apheresis device using a central venous catheter. During the stem cell collection stage, granulocyte colony-stimulating factor (G-CSF) was administered at a dose of 10 mcg/kg to the patients. Enough cells for two transplants were collected and cryopreserved. 8-12 mCi/kg dose of MIBG was given to the patients who completed the induction treatment and underwent surgery. The first transplantation was performed with conditioning regimen consisting of busulfan and melphalan 3 weeks after the first MIBG.

MIBG was repeated at a dose of 8-12 mCi/kg after first autologous HSCT in patients. In the second autologous HSCT, a conditioning regimen containing melphalan, etoposide and carboplatin was used. Nine cycles of 13-cis retinoic acid were given in the post-transplant maintenance treatment (**Figure 1**).

**Statistical Analysis**

Categorical data were expressed as the number of patients and percentage and continuous variables were expressed as the mean±standard deviation or median (minimum-maximum). Nominal variables were expressed as number of cases and percentage (%). The Kaplan-Meier method was used to estimate survival probabilities.

**RESULTS**

The median age of 11 patients (8 boys, 3 girls) included in the study was 40.5 (range, 22.1-72.9) months. The clinical features of the patients are summarized in **Table 1**.

The median value of CD34 (+) cell count in the stem cell product given in the first transplantation was 7.5 (range, 4.55-17.1) ×10<sup>6</sup> cells/kg. The median day of

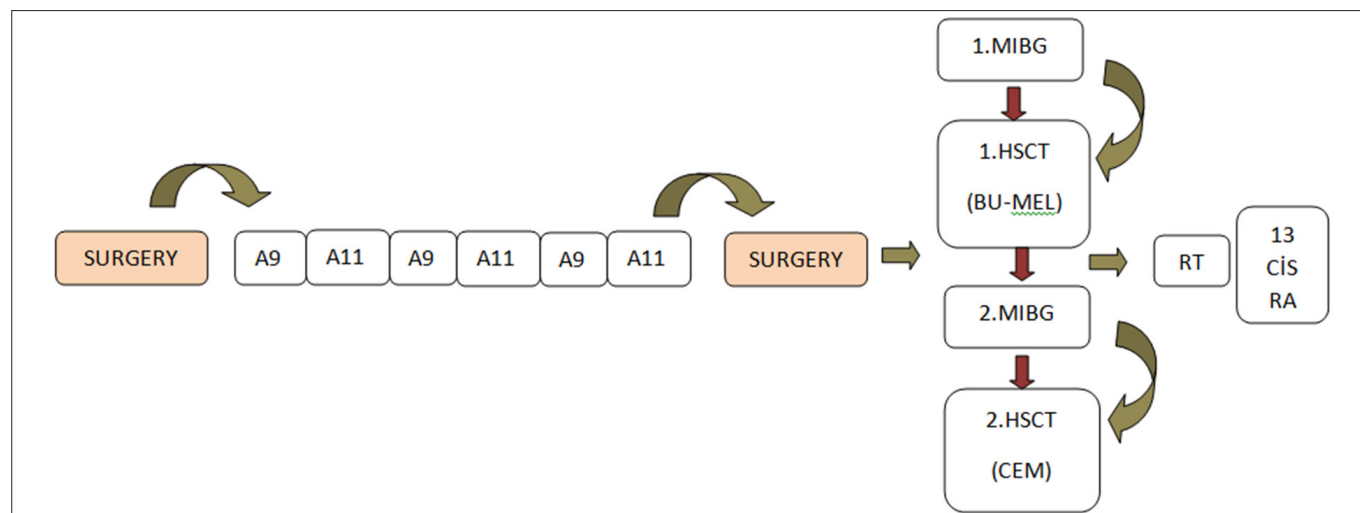
myeloid and platelet engraftment was detected as +12 (9-22) days and +18 (12-28) days, respectively. The mean time between two HSCT was 4.7±0.5 months. In the second HSCT, 5.7 (2.7-16.7) ×10<sup>6</sup> cells/kg CD34(+) cells were given. The median day of myeloid and platelet engraftment was +11 (9-15) days and +19 (16-21) days, respectively.

Only one patient did not have bone metastases at the time of diagnosis (Patient 6). One patient died on the 45<sup>th</sup> day of the second transplantation due to venoocclusive disease and sepsis, and 4 patients died due to progressive disease. Transplant-related mortality was 4.5%. After the second HSCT, 3 patients (Patient 9, 10, and 11) with residual tumors were given radiotherapy for local control. Retinoic acid maintenance therapy was given to the surviving patients (Patient 2, 5, 8, 9, 10, and 11).

In our study, the overall survival rate (OS) was 54.5% and event-free survival (EFS) was 39% at a median follow-up of 20.7 (range, 7.8-105.6) months (**Figure 2**). Of the 6 surviving patients, 4 are followed in complete remission and 2 in partial remission (**Table 1**).

**Table 1.** Patient characteristics

Patient number	Sex	Diagnosis age (month)	Tumor type	Histology	Stage	N-Myc	Outcome
1	Boy	26.7	Ganglioneuroblastoma	Poorly Differentiated	4	Amplified	Exitus
2	Boy	24.4	Neuroblastoma	Intermixed	4	Amplified	Remission
3	Boy	24	Neuroblastoma	Undiferantiated	4	Not amplified	Exitus
4	Girl	35.9	Neuroblastoma	Undiferantiated	4	Not amplified	Exitus
5	Boy	45.6	Neuroblastoma	Undiferantiated	4	Not amplified	Remission
6	Boy	13.7	Neuroblastoma	Undiferantiated	4	Amplified	Exitus
7	Girl	88.2	Neuroblastoma	Undiferantiated	4	Not amplified	Exitus
8	Girl	31.7	Ganglioneuroblastoma	Poorly Differentiated	4	Not amplified	Remission
9	Boy	13.1	Neuroblastoma	Undiferantiated	4	Amplified	Remission
10	Boy	33.8	Neuroblastoma	Poorly Differentiated	4	Amplified	Partial Remission
11	Boy	48.8	Ganglioneuroblastoma	Poorly Differentiated	4	Not amplified	Partial Remission



**Figure 1.** Treatment scheme

A9: Vincristine, dacarbazine, ifosfamide, adriamycin; A11: Cyclophosphamide, etoposide, cisplatin; Bu: Busulfan; Mel: Melphalan; CEM: Carboplatin, etoposide, melphalan; HSCT: Hematopoietic stem cell transplantation; MIBG: Iodine 131 (131I) metaiodobenzylguanidine ; RT: Radiotherapy; 13 CIS RA: 13-cis retinoic acid

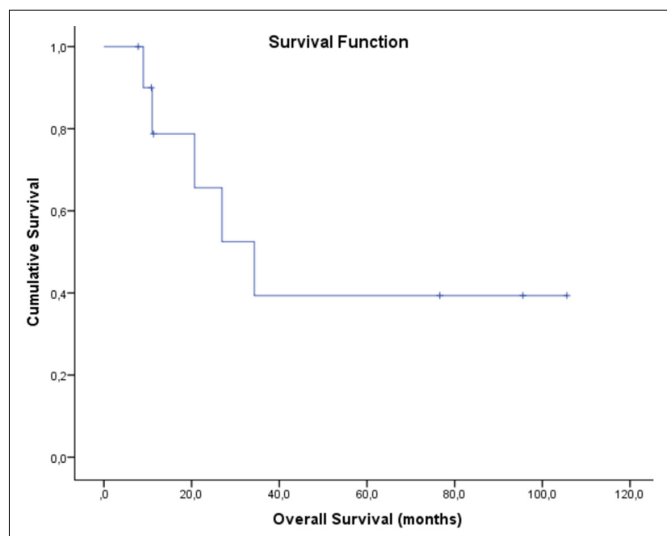


Figure 2. Overall survival of patients

### DISCUSSION

Neuroblastoma is related to the disproportionate morbidity and mortality among the cancers of childhood and has been shown that high-dose chemotherapy with autologous stem cell rescue has improved the outcomes for children with high-risk neuroblastoma (8,18). In non-metastatic patients, chemotherapy, surgery, and/or radiotherapy are often cured. However, 40% of these patients are high-risk or ultra high-risk cases which is extremely difficult to provide cures for these patients. The current therapies including high-dose chemotherapy and HSCT are border on tolerability limits with insufficient effectiveness. Therefore, alternative protocols aiming at curative treatment are required.

The high-risk tumors include a heterogeneous group of patients with a wide range of outcome spectrum. Treatment of 5 phases with high-risk tumors includes; induction, surgery, metastatic remission, myeloablative chemotherapy with autologous HSCT, radiotherapy, and biological differentiation therapy (19). Main modalities have been standardized however, autologous HSCT

approaches vary considerably. In the literature, autologous HSCT was performed with MIBG to be applied once to patients in the high-risk group, and the overall response rate was found to be 27% with the 31% 3-year EFS (20). In 2012, Qayed et al., showed that patients who were randomized to high dose chemotherapy and HSCT had a significantly improved at 3-year EFS compared with high dose chemotherapy and HSCT (4-year EFS 59.3±6.7% vs. 26.8±9.2%, p=0.01) (21). The Children’s Oncology Group (COG) Phase 3 trial (NCT00567567) compared carboplatin-etoposide-melphalan and thiotepa based tandem HSCT. They found significantly increased 3 year EFS (3-year) scores (61.8% versus 48.8%; p=.0082) (14). Follow up results of this randomized controlled trial data in 2019 comparing tandem and single transplants show 85 of 176 tandem HSCT were in complete remission/very good partial response, and 121 of 176 were needed immunotherapy (8). Another immunologically based study compared post-transplant dinutuximab beta effects was also concluded that improved EFS (5-year) results with superior significant improvement in OS (5-year) (66.7% versus 11.4%; p=.0007) (22). Major tandem studies are summarized in **Table 2** (8,23-27). The experience of allogeneic HSCT in high-risk neuroblastoma patients is increasing over time (27,28).

In our study, the overall survival rate of ultra high-risk patients was 54.5% and EFS was 39% without cytokine and immunotherapies. In our patients with minimal toxicity, this tandem treatment modality provides encouraging results. Our results appear to be better than the previously high-risk studies eventhough immunotherapies were not used at all. MIBG is an adrenal imaging analogue marker initially developed at the University of Michigan fifty years ago; however, by the time with studies as therapy has directed on palliation for patients with refractory disease. The majority of authors focusing on patients with MIBG avid, non-responsive or progressive disease with safety profile, and also potential efficacy

Study	Patient	Pre-transplant remission status	Conditioning regimen	Additional treatment	OS	EFS
Park et al.	176	PR, CR, MR	Cy-TT/CEM	RT, 13 Cis RA, IT	74% (3-year)	61% (3-year)
Pasqualini et al.	26	PR, CR	TT/ Bu-Mel	RT, 13 Cis RA	69% (3-year)	37.3% (3-year)
Suh et al.	18	PR, CR, MR	CEM/Bu-Mel/TT-Cy	RT, 13 Cis RA, single MIBG, IT	83% (5-year)	64% (5-year)
Lee et al.	54	PR, CR, MR	CEC/TT-Mel	RT, 13 Cis RA, single MIBG, IT	72.4% (5-year)	58.3% (5-year)
Sung et al.	50	PR, CR, MR	CEC/TT-Mel-TBI/TT-Mel	RT, 13 Cis RA, IT	77% (5-year)	71.4% (5-year)
George et al.	82	-	CEC/TBI-Mel	RT, 13 Cis RA	64% (5-year)	54%(5-year)-PFS
Our Data	11	PR, PD	Bu-Mel/CEM	RT, 13 Cis RA, tandem MIBG	54.5% (3-year)	39% (3-year)

CR: Complete response, PR: Partial response, MR: Mixed response, PD: Progressive disease, TT: Thiotepa, Bu: Busulfan, Mel: Melphalan, TBI: Total body irradiation, CEM: Carboplatin, etoposide, melphalan, CEC: Carboplatin, etoposide, cyclophosphamide, Cy: Cyclophosphamide, RT: Radiotherapy, 13 Cis RA: 13 Cis retinoic acid, MIBG: Iodine 131 (<sup>131</sup>I) metaiodobenzylguanidine, IT: Immunotherapy, PFS: Progression free survival, OS: Overall survival, EFS: Event free survival



of this regimen, the combination of chemotherapy and stem cell rescue is being considered within COG for the refractory neuroblastoma patients (29). As a result, our study suggested that tandem MIBG and tandem autologous HSCT combination might indeed improve the EFS of the ultra high-risk refractory patients.

The limitations of the study were that it is retrospective design and the sample is relatively small. In addition, the patients were not given cytokine and immunotherapy/anti-GD2 antibodies. Survivors should be evaluated for any toxicity.

## CONCLUSION

This study is the only case series study with both tandem high-dose MIBG and tandem autologous HSCT transplantation in refractory NBL patients without cytokine and immunotherapy. Tandem transplantation and MIBG therapy in ultra high-risk NBL cases remain promising with acceptable toxicity. Our data show that a significant contribution may be added to the survival of ultra high-risk NBL patients based on this dual protocol. Adding immunotherapy to this treatment protocol and combining it with new treatment modalities such as anaplastic lymphoma kinase (ALK), which also takes into account genetic characteristics, may increase survival and EFS rates.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Erciyes University Faculty of Medicine Clinical Researchs Ethics Committee (Date: 08.07.2020, Decision No: 2020/371).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

**Acknowledgment:** The authors thank Prof. Dr Mehmet Akif Özdemir, Prof. Dr. Türkan Paturoğlu for their valuable contributions to the study.

## REFERENCES

- Swift CC, Eklund MJ, Kravaka JM, Alazraki AL. Updates in Diagnosis, Management, and Treatment of Neuroblastoma. *Radiographics* 2018; 38: 566-80.
- Schwab M, Shimada H, Joshi V, Brodeur GM. Neuroblastic tumours of adrenal gland and sympathetic nervous system. In: Pathology and Genetics. Tumours of the Nervous system, Kleihues P, Cavenee WK (eds). IARC Press: Lyon; 2000: 153-61.
- Smith V, Foster J. High-risk neuroblastoma treatment review. *Children (Basel)* 2018; 5: 114.
- Almandoz JP, Xie L, Schellinger JN, et al. Impact of COVID-19 stay-at-home orders on weight-related behaviours among patients with obesity. *Clin Obes* 2020; 10: e12386.
- Kebudi R. Turkish Pediatric Oncology Group. Pediatric oncology in Turkey. *J Pediatr Hematol Oncol* 2012; 34: S12-4.
- Louis CU, Shohet JM. Neuroblastoma: molecular pathogenesis and therapy. *Annu Rev Med* 2015; 66: 49-63.
- Zhang Y, Huang D, Zhang W, et al. Clinical characteristics of infant neuroblastoma and a summary of treatment outcome. *Oncol Lett* 2016; 12: 5356-62.
- Park JR, Kreissman SG, London WB, et al. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: a randomized clinical trial. *JAMA* 2019; 322: 746-55.
- Pinto NR, Applebaum MA, Volchenbom SL, et al. Advances in risk classification and treatment strategies for neuroblastoma. *J Clin Oncol* 2015; 33: 3008-17.
- Smith V, Foster J. High-risk neuroblastoma treatment review. *Children (Basel)* 2018; 5.
- Aygün Z, Batur Ş, Emre Ş, Celkan T, Özman O, Comunoglu N. Frequency of ALK and GD2 expression in neuroblastoma. *Fetal Pediatr Pathol* 2019; 38: 326-34.
- Morgenstern DA, Bagatell R, Cohn SL, et al. The challenge of defining "ultra-high-risk" neuroblastoma. *Pediatr Blood Cancer* 2019; 66: e27556.
- Berthold F, Spix C, Kaatsch P, Lampert F. Incidence, survival, and treatment of localized and metastatic neuroblastoma in Germany 1979-2015. *Paediatr Drugs* 2017; 19: 577-93.
- Park JR, Kreissman SG, London WB, et al. A phase III randomized clinical trial (RCT) of tandem myeloablative autologous stem cell transplant (ASCT) using peripheral blood stem cell (PBSC) as consolidation therapy for high-risk neuroblastoma (HR-NB): A Children's Oncology Group (COG) study. *J Clin Oncol* 2016; 34.
- Kushner BH, Ostrovnaya I, Cheung IY, et al. Lack of survival advantage with autologous stem-cell transplantation in high-risk neuroblastoma consolidated by anti-GD2 immunotherapy and isotretinoin. *Oncotarget* 2016; 7: 4155.
- Kushner BH, Cheung NK, LaQuaglia MP, et al. International neuroblastoma staging system stage 1 neuroblastoma: a prospective study and literature review. *J Clin Oncol* 1996; 14: 2174-80.
- Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 1993; 11: 1466-77.
- Elborai Y, Hafez H, Moussa EA, et al. Comparison of toxicity following different conditioning regimens (busulfan/melphalan and carboplatin/etoposide/melphalan) for advanced stage neuroblastoma: Experience of two transplant centers. *Pediatr Transplant* 2016; 20(2): 284-9.
- Bansal D, Totadri S, Chinnaswamy G, et al. Management of neuroblastoma: ICMR consensus document. *Indian J Pediatr* 2017; 84: 446-55.
- Matthay KK, Tan JC, Villablanca JG, et al. Phase I dose escalation of iodine-131-metaiodobenzylguanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: a new approaches to Neuroblastoma Therapy Consortium Study. *J Clin Oncol* 2006; 24: 500-6.
- Qayed M, Chiang KY, Ricketts R, et al. Tandem stem cell rescue as consolidation therapy for high-risk neuroblastoma. *Pediatr Blood Cancer* 2012; 58: 448-52.

22. Wawrzyniak-Dzierżek E, Gajek K, Rybka B, et al. Feasibility and safety of treosulfan, melphalan, and thiotepa-based megachemotherapy with autologous or allogeneic stem cell transplantation in heavily pretreated children with relapsed or refractory neuroblastoma. *Biol Blood Marrow Transplant* 2019; 25: 1792-7.
23. Pasqualini C, Dufour C, Goma G, Raquin MA, Lapierre V, Valteau-Couanet D. Tandem high-dose chemotherapy with thiotepa and busulfan-melphalan and autologous stem cell transplantation in very high-risk neuroblastoma patients. *Bone Marrow Transplant* 2016; 51: 227-31.
24. Suh JK, Koh KN, Min SY, et al. Feasibility and effectiveness of treatment strategy of tandem high-dose chemotherapy and autologous stem cell transplantation in combination with <sup>131</sup>I-MIBG therapy for high-risk neuroblastoma. *Pediatr Transplant* 2020; 24: e13658.
25. Lee JW, Lee S, Cho HW, et al. Incorporation of high-dose <sup>131</sup>I-metaiodobenzylguanidine treatment into tandem high-dose chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma: results of the SMC NB-2009 study. *J Hematol Oncol* 2017; 10: 108.
26. Sung KW, Son MH, Lee SH, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk neuroblastoma: results of SMC NB-2004 study. *Bone Marrow Transplant* 2013; 48: 68-73.
27. George RE, Li S, Medeiros-Nancarrow C, et al. High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update. *J Clin Oncol* 2006; 24: 2891-6.
28. Erbey F, Atay D, Akçay A, Öztürk G. Autologous cord blood transplantation in neuroblastoma. *Turk J Pediatr* 2015; 57: 210-1.
29. Grupp SA, Asgharzadeh S, Yanik GA. Neuroblastoma: issues in transplantation. *Biol Blood Marrow Transplant* 2012; 18: S92-100.