Original Article

Treatment of high-risk neuroblastoma: National protocol results of the Turkish Pediatric Oncology Group

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ABSTRACT

Background: The national protocol aimed to improve the outcome of the high risk neuroblastoma patients by high-dose chemotherapy and stem cell rescue with intensive multimodal therapy.

Materials and Methods: After the 6 induction chemotherapy cycles, patients without disease progression were nonrandomly (by physicians' and/or parent's choices) allocated into two treatment arms, which were designed to continue the conventional chemotherapy (CCT), or myeloablative therapy with autologous stem cell rescue (ASCR).

Results: Fifty-six percent (272 patients) of patients was evaluated as high risk. Response rate to induction chemotherapy was 71%. Overall event-free survival (EFS) and overall survival (OS) at 5 years were 28% and 36%, respectively. "As treated" analysis documented postinduction EFS of 41% in CCT arm ($n = 138$) and 29% in ASCR group ($n = 47$) ($P = 0.042$); whereas, OS was 45% and 39%, respectively ($P = 0.05$). Thirty-one patients (11%) died of treatment-related complications.

Conclusion: Survival rates of high-risk neuroblastoma have improved in Turkey. Myeloablative chemotherapy with ASCR has not augmented the therapeutic end point in our country's circumstances. The adequate supportive care and the higher patients' compliance are attained, the better survival rates might be obtained in high-risk neuroblastoma patients received myeloablative chemotherapy and ASCR.

KEY WORDS: Autologous stem cell rescue, high-risk neuroblastoma, treatment, Turkey

INTRODUCTION

Neuroblastoma, is an embryonal neoplasm of the sympathetic nervous system arising from the neural crest, is the most extracranial malignant solid tumor in children, accounting for 8% to 10% of all childhood cancers and for approximately 15% of cancer deaths in children. Outcomes for low- and intermediate-risk neuroblastoma are excellent, but patients with high-risk tumors have dismal outcome despite aggressive therapy. The current therapeutic regimens used for high-risk patients throughout the world generally have three components: Induction therapy, consolidation therapy (currently using myeloablative chemotherapy with autologous stem cell rescue [ASCR]), and maintenance aimed at the minimal residual disease.[1,2]

Risk-based national neuroblastoma treatment protocol (TPOG-NBL2003) was designed in Turkey in 2003, and it was applied until 2010. The original intent was to improve treatment results of the advanced disease and decrease the related side effects. The main objective of the study was not to compare the treatment arms, only to determine the feasibility of intensive treatment strategies for neuroblastoma in Turkish healthcare conditions.

Access this article online	
Website: www.cancerjournal.net	Quick Response Code:
DOI: 10.4103/0973-1482.183205	

Cite this article as: Aksoylar S, Varan A, Vergin C, Hazar V, Akici F, Dagdemir A, *et al*. Treatment of high-risk neuroblastoma: National protocol results of the Turkish Pediatric Oncology Group. J Can Res Ther 2017;13:284-90.

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MATERIALS AND METHODS

Patients

Neuroblastoma is the most common extra-cranial solid tumor in children comprising 7.4% of all childhood cancers in Turkey. Five hundred and fifty-nine children with neuroblastoma (0–21 years) from 34 pediatric oncology centers in Turkey were registered in the national protocol (TPOG-NBL2003) between October 2002 and October 2010. Registered cases constituted approximately 90% of neuroblastoma patients according to the epidemiologic survey from the Turkish Pediatric Cancer Registry.[3] "International Neuroblastoma Pathology Classification (INPC)" was used for the histopathologic diagnosis of neuroblastoma and the staging was performed in accordance with the International Neuroblastoma Staging System criteria.[4,5] Risk assessment was defined using Children's Oncology Group criteria (without ploidy) and cases were considered at high risk if they had Stage 4 disease and were older than 1 year, or Stage 3 disease with unfavorable histology plus older than 1 year, or Stage 2 (older than 1 year), 3, 4 or 4 S disease with MYCN amplification.[6-8] MYCN gene amplification was determined by fluorescence *in situ* hybridization in a central laboratory and a >10 copies per haploid genome was defined as MYCN amplification. Risk stratification of the patients with undetermined MYCN status was evaluated by age, stage, and histology.[9]

Initial evaluation of the patients included computed tomography or magnetic resonance imaging of the primary tumor with 99mTc bone scan, skeletal survey, bone marrow aspirates and biopsies, and metaiodobenzylguanidine scan (MIBG) was strongly recommended if available. Urinary catecholamines, serum lactic dehydrogenase, ferritin, and neuron-specific enolase values were also analyzed.

Treatment

After the surgery or biopsy, high-risk patients received intensified induction chemotherapy which consisted of alternating cycles of A3 and A5, at 3 weeks intervals [Table 1]. Administration of granulocyte colony-stimulating factor (G-CSF) was recommended after each chemotherapy cycle. After an induction of 6 alternating A3 and A5 cycles, high-risk patients without disease progression were nonrandomly (by physicians' and/or parent's choices) allocated into two treatment arms which were designed to continue the intensive conventional chemotherapy (CCT), or initiate myeloablative therapy with ASCR. The decision taken not by only the physicians' preference and center's facility, but also the parent's consent and socio-economic situation of the family to transport to another institution of the TPOG where ASCR facility existed [Figure 1].

Surgery was performed at diagnosis or after four or six cycles of chemotherapy. Second and third look operations were encouraged if feasible. Radiotherapy was recommended to the primary and all bulky metastasis following induction chemotherapy and surgery, and total dose was modulated by age (25 Gy ≤ 2 years and 35 Gy > 2 years).

Table 1: Chemotherapy regimens on Turkish Pediatric Oncology Group Neuroblastoma 2003

Chemotherapy	Drug	Schedule
Induction cycles A3	Vincristine	1.5 mg/m²/day on days 1 and 5, IV push
	Ifosfamide	1.8 g/m²/day on days 1-5, IV-continue infusion
	Dacarbazine	250 mg/m²/day on days 1-5, IV 30 min
	Adriamycin	20 mg/m²/day on days 1-3, IV over 4 h
A5	Cisplatin	30 mg/m²/day on days 1-5, IV-continue infusion
	Cyclophosphamid	300 mg/m²/day on days 1-5, IV over 1 h
	Etoposide	150 mg/m²/day on days 4 and 5, IV 1 h
Consolidated maintenance (3 weeks interval)	Vincristine	1.5 mg/m²/day on day 1, IV push
	Cyclophosphamid	400 mg/m²/day on days 1-3, IV over 1 h
	Carboplatin	150 mg/m²/day on days 1-2, IV over 1 h
Differentiating maintenance (2 weeks interval)	13-cis-retinoic acid	160 mg/m²/day on days 1-14 PO
Myeloablative conditioning days−7-−4	Carboplatin	300 mg/m²/day IV-continue infusion
	Etoposide	200 mg/m²/day IV-continue infusion
	Melphalan	50 mg/m²/day IV over 30 min

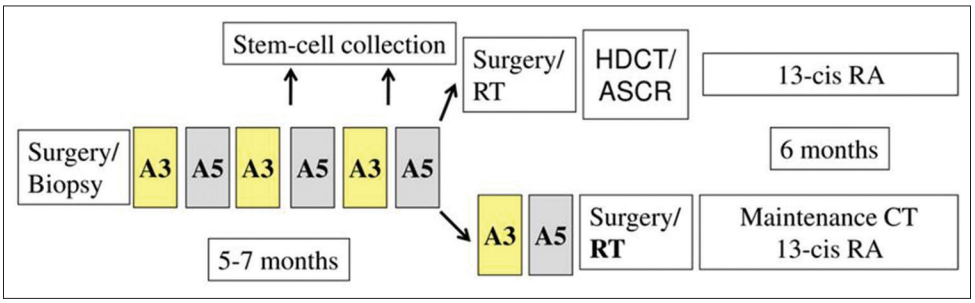

Figure 1: Flow chart of treatment (A3, A5: Chemotherapy cycles, RT: Radiotherapy, HDCT: High dose chemotherapy, ASCR: Autologous stem cell rescue, CT: Chemotherapy, RA: Retinoic acid)

Peripheral blood stem cells were collected in ASCR group without progressive disease (PD), after the third or fifth cycle of chemotherapy. CD34-positive stem cell count was targeted to be equal or higher than 2×10^6 per kg of body weight for reinfusion. Purging was not recommended.

Myeloablative therapy was applied to the ASCR group who responded to the treatment after the 6th cycle of chemotherapy and surgery. After the stem cell transfusion, G-CSF (10 μg/kg/day) was introduced at day +1 until the acid neutralizing capacity reached 1000/ml. Maintenance was supplied with six cycles of 13-cis-retinoic acid during the posttransplant period [Figure 1].

Patients in the CCT group continued A3 and A5 alternating blocks of induction chemotherapy for 8 cycles and then delayed surgery and radiotherapy of the primary tumor were performed as was done in the ASCR group. For patients in whom very good partial remission (VGPR) or PR were achieved, chemotherapy blocks were extended to 10 cycles. Consolidated maintenance treatment was also given with 13-cis-RA for 6 months in CCT group [Figure 1 and Table 1].

Treatment response was evaluated by International Neuroblastoma Response Criteria after the second and last cycle of induction chemotherapy, at the time of completion of the continuation chemotherapy or transplantation, or at any time when disease progression was suspected.

Toxicity was scored according to the World Health Organization toxicity guidelines.

Statistics

Survival rates for all patients were measured from the date of diagnosis to death or to the last contact with the surviving patients. Event-free survival (EFS) was calculated from the date of diagnosis to the first event (death from any cause, tumor progress, or second malignancy) or to the last follow-up. Patients lost to follow-up were censored at the time of their withdrawal. Differences in the distribution of parameters were examined using the χ^2 or Fisher exact test. Survival curves were constructed by the Kaplan–Meier method with differences compared using the log-rank test.

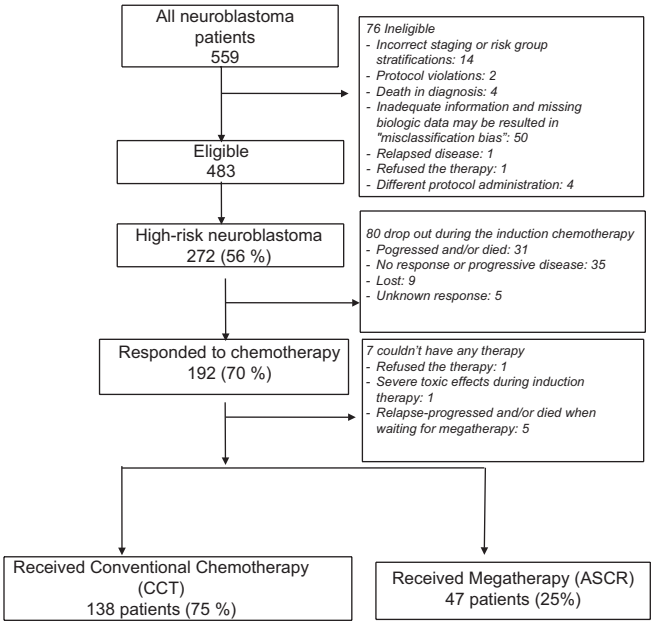

Figure 2: Trial profile

The comparison of the treatment regimens was done according to the "as treated" analysis. The comparison was performed at the end of six cycles of induction chemotherapy, postinduction EFS, and overall survival (OS) were evaluated among patients who responded the induction chemotherapy. The "as-treated" group was defined by the treatment received independently of the assigned groups.

Statistical analysis was performed using SPSS® 13.0, (SPSS Inc., IBM SPSS, Chicago, IL, United States) for PC.

RESULTS

Patient characteristics

Of the 559 registered neuroblastoma cases, 76 cases were ineligible [Figure 2] and 483 children were enrolled in TPOG-NBL2003. Among patients whose missing biologic data (MYCN or INPC) might have resulted in "misclassification bias" were excluded from the study. However since advanced stages were well-documented, risk stratification was held by age as was a histopathological classification in patients with unknown MYCN status.

Table 2: Baseline characteristics of all neuroblastoma patients and the patients who participated for the "as treated" analysis after the 6 cycles induction chemotherapy on conventional chemotherapy and autologous stem-cell rescue groups

	All patients, *n* (%)	CCT, *n* (%)	ASCR, *n* (%)	*P*
Overall eligible	272	138	47	
Age (months)				
<12	7 (2)	3 (2)	2 (4)	0.45
12-18	29 (11)	16 (12)	8 (17)	
>18	236 (87)	119 (86)	37 (79)	
Stage (INSS)				
2A	2 (1)	1 (1)	1 (2)	0.21
3	45 (16)	29 (21)	5 (10)	
4	224 (82)	108 (78)	41 (88)	
4S	1 (1)	-	-	
MYCN amplification				
Yes	46 (17)	17 (12)	10 (21)	0.013
No	74 (27)	34 (25)	19 (40)	0.55 (yes vs. no)
Unknown	152 (56)	87 (63)	18 (38)	
Histopathology				
Favorable	15 (6)	8 (6)	3 (6)	0.63
Unfavorable	152 (55)	75 (54)	26 (55)	
Unknown	105 (39)	55 (40)	18 (39)	
Primary tumor site				
Suprarenal	200 (73)	103 (74)	37 (79)	0.68
Other abdomino pelvic	37 (14)	24 (18)	5 (11)	
Cervical-thoracic	15 (6)	7 (5)	1 (2)	
Multiple primary tm	12 (4)	3 (2)	3 (6)	
No known primary	6 (2)	1 (1)	-	
Other	2 (1)	-	1 (2)	
LDH (U/L)				
>1500	95 (35)	45 (32)	13 (28)	0.46
<1500	147 (54)	75 (55)	30 (64)	
Unknown	30 (11)	18 (13)	4 (8)	
Bone metastasis				
Absent	109 (40)	65 (47)	16 (34)	0.2
Present	153 (56)	67 (48)	30 (64)	
Unknown	10 (4)	6 (5)	1 (2)	
Response to induction chemotherapy				
Complete/or very good partial remission	73 (27)	51 (37)	19 (40)	0.51
Partial remission	119 (44)	87 (63)	28 (60)	
No response or progressive disease	35 (13)			
Died in induction	31 (11)			
Lost or unknown response	14 (5)			

INSS=International Neuroblastoma Staging System, LDH=Lactic dehydrogenase, CCT=Conventional chemotherapy, ASCR=Autologous stem-cell rescue

Fifty-six percent ($n = 272$) of the group was evaluated as high risk [Figure 2]. The median age at diagnosis was 3 years (range: 2 months–17.5 years) with 1.06 male/female ratio (140 male, 132 female). Patient characteristics are shown in Table 2.

Overall 77% of the patients were diagnosed on the basis of pathologic examinations of tumor samples, and 23% by the results of bone marrow investigations combined with elevated levels of urinary catecholamines. MIBG was performed in 143 cases (52%).

Treatment

Primary surgery at diagnosis was performed in 18% of the patients and complete resection was in 4% of them. "Early death" was observed in 12 (4%) patients within the 1st month of the therapy. Totally 31 patients progressed and/or died and 35 patients, not responded or progressed through induction chemotherapy, nine patients were lost to follow-up within this period of the therapy [Figure 2]. The treatment-associated deaths were 5% (14 patients) of the patients during the induction.

Treatment response to the induction chemotherapy was evaluated in whole 272 high-risk patients and complete remission (CR)/VGPR and PR were achieved in 27% ($n = 73$) and 44% ($n = 119$) of the patients, respectively [Table 2]. Delayed surgery was performed in 63% of the patients, and complete resection was achieved in 25% of them. Nineteen percent of the patients either did not receive any surgical treatment due to various reasons (no visible tumor residue after chemotherapy, deceased/progressed during induction) or there was missing data on surgery. Local radiotherapy to the primary residual tumor was given in 52% ($n = 100$) of the surviving patients without disease progression at the end of induction chemotherapy.

A total of 192 patients completed induction chemotherapy without disease progression. Of this group, 138 were in CCT and 54 planned to receive mega therapy. Patient characteristics were similar in CCT and ASCR groups except

there was more missing MYCN data in CCT group. There was no difference between groups according to the induction response ($P = 0.51$) [Table 2].

Myeloablative chemotherapy and autologous stem cell rescue

Of the patients in the ASCR group ($n = 54$) one patient refused myeloablative therapy and ASCR could not be held in one patient because of severe toxicity of the induction course. While 5 patients responded to induction chemotherapy (VGPR in 1, PR in 4 patients), the disease progressed during the median 7 months (range: 7–9 months) from the diagnosis while on the waiting list for myeloablative therapy and ASCR. The median time between last induction cycle to the time disease progression was observed was 13 weeks (range: 7–14 weeks) in those patients. While on the waiting list, 8 patients received an additional cycle of chemotherapy. Finally, myeloablative chemotherapy followed by stem cell rescue was performed in 47 cases [Figure 2].

Thirty-nine patients were transplanted who demonstrated CR/VGPR, and 8 were transplanted showing PR. The transplant procedure was held in eight centers in Turkey. The time from diagnosis to ASCR varied from 5 to 16 months, with a median of 8 months. Carboplatin, etoposide and melphalan (CEM) were used for myeloablative conditioning [Table 1]. The stem cell source was the peripheral blood in 37 patients, bone marrow in 8 patients and peripheral blood plus bone marrow in 2 patients. All patients, except one, engrafted at a median of 13 days after the stem cell infusion. Eight patients (17% of the transplanted patients) died during the early posttransplantation period due to transplant-related complications.

Outcome

In all high-risk patients during the entire therapy period; 121 patients (44%) relapsed or demonstrated PD at 13 months (median, range: 2–56 months) from diagnosis. Relapses occurred from the primary sites in 18%, from the nonprimary in 38% and from both in 24% of the patients.

At the time of analysis, the median follow-up time was 45 months, and of the 102 (38%) patients still alive, 86 were in CR and 16 had the disease. One hundred and forty-eight of the patients died while 22 were lost to follow-up (8 in CR/VGPR, 3 in PR, 11 in NR/PD or in relapse) at 10 months (median, range: 1–34 months). One hundred and six patients died of tumors and 31 patients (11% of the all high-risk patients) died of treatment-related complications (chemotherapy-related: 21, surgery related: 1, transplantation-related: 8, secondary tumor: 1, pulmonary hypertension: 1, unknown: 10 patients).

The treatment-associated deaths were slightly higher in transplantation group, but this is not significant 6% of which were in the CCT group and 14% of which were in the ASCR group ($P = 0.07$).

Survival

The 5 years EFS of all 272 patients was 28% and the 5 years OS was 36%.

The results of the "as-treated" analysis were that; after the induction 5 years OS was 45% and 5 years EFS was 41% for the CCT group, while the 5 years OS was 39% and EFS was 29% for the ASCR group (log-rank *P* for EFS 0.042 and for OS 0.05).

DISCUSSION

Treatment of high-risk neuroblastoma remains one of the greatest challenges in pediatric oncology. During the past 30 years, increasingly intensive, multimodality approaches have been developed to treat patients who are classified as high risk. This treatment approach has resulted in improved outcome, although survival for high-risk patients remains poor, emphasizing the need for more effective treatments. Increased knowledge regarding the biology and genetic basis of neuroblastoma has led to the discovery of druggable targets and promising, new therapeutic approaches.[10]

The 5 years EFS of all high-risk patients was 28% and 5 years OS was 36% with our national treatment protocol which was applied between 2003 and 2010. Former protocol (IPOG-NBL-92) from the western part of Turkey had documented a long-term survival rate of 5% for Stage 4 disease.[10,11] However, IPOG-NBL-92 protocol had some drawbacks because the patient protocol was based on a restricted part of the country and advanced disease was determined solely by staging. The current protocol corrected these disadvantages using a nationwide distribution of patients, with risk based on treatment strategy, and additionally assessed autologous ASCR therapy compared to conventional treatment. The long-term survival rate in those at high risk was significantly improved with TPOG-NBL 2003 protocol. Factors such as more effective regimen, improved surgical techniques, better supportive care, and socio-economic changes in the country may have contributed to these improved results. Even though, better results were achieved and approximately 90% of Turkish neuroblastoma cases were included; missing biological data might have caused "misclassification bias" and inadequate data collection resulted in almost 9% drop-outs from the whole study group. Reports on toxicity were not adequate except for severe toxicity or toxic death so that minor toxicity could not be evaluated. Moreover, MYCN and histopathological prognostic classification (INPC) were missing in approximately 55–40% of the cases, respectively, due to the inadequate tissue sample and insufficient communication between pediatric surgeons and pediatric oncologists, as well as transportation errors around the country.

High-risk neuroblastoma is generally sensitive to initial chemotherapy, but despite chemotherapy dose intensification and improvements in complete response rates, approximately 20% of patient will progress or have an inadequate response to induction therapy.[11,12] Response rate to induction

chemotherapy was 71% in our protocol. Thirty-one patients progressed and/or died (12 of them died within the 1st month of therapy) during the induction phase and 9 patients were lost to follow-up within the early period of therapy.

The role of dose intensification to overcome tumor drug resistance mechanisms followed by bone marrow or peripheral blood stem cell support has been investigated for more than 20 years.[13] Retrospective studies mostly suggest that intensification of consolidation therapy with ASCR following high-dose chemotherapy improves survival.[14-16] The results of nonrandomized pilot studies by the Children's Cancer Group also suggest a modest prolongation of EFS for children with high-risk of neuroblastoma.[16,17] On the other hand, all three randomized studies in the literature and a recent meta-analysis identified a significant difference of EFS in favor of the transplant group.[12,18-21] Importantly, for OS, there is no evidence of a better outcome in patients treated with myeloablative therapy.[20-22]

In Turkey, when this study was taking place the transplant facilities were not provided in every oncology center, neither could all patients transfer to transplant centers, nor was the present capacity of transplant centers were capable of handling all these patients. All these factors contributed to this nonrandomized study design. The primary objective of this study was not to compare the treatment arms, only to determine the feasibility of intensive treatment strategies for neuroblastoma in Turkish healthcare conditions. Despite the fact that the study design negatively affects the integrity of the comparison between the two treatment modalities, this study showed a similar survival for patients given intensified chemotherapy compared to patients receiving myeloablative chemotherapy with ASCR. Moreover, better EFS was obtained in the CCT group than in the myeloablative chemotherapy with ASCR. The inferior outcome of ASCR group in this study might be related to the design of the study. For instance, we know that there will be a bias in the selection of patients to ASCR as more high-risk patients may be selected for the aggressive ASCR. Furthermore, MYCN was only available in 44% of patients and lacking MYCN data were more in CCT group. There may be an uneven distribution of MYCN patients in the two groups and which may have a great impact on the outcome. The ASCR group also had a higher percentage of Stage 4 disease and bone metastasis, although these were not statistically significant because the sample groups might have been not enough in numbers to show the difference. There was also high transplant-related mortality during those years (17%) which also contributed to the inferior result.

A total treatment-related mortality was 11% in our study. In a German study, treatment-related deaths were only 3%.[18] Eight patients given myeloablative chemotherapy died from acute complications related to mega-therapy. The treatment-associated deaths were slightly higher in transplantation group, but this is not significant. Recently, a meta-analysis of treatment-related deaths did not show a significant difference between the treatment groups.[22]

The conditioning of ASCR in this study was CEM. In the recent European randomized clinical trial, busulfan/melphalan (BuMel) was shown to have better outcome.[23] A significant difference in EFS in favor of BuMel (3 years EFS 49% vs. 33%) was observed as well as for OS. Relapse and progression incidence was significantly lower with BuMel and the severe toxicity rate up to day 100 was significantly higher for CEM. Based on these results; BuMel was recommended as standard treatment.

Variable supportive care conditions of the oncology and transplantation centers in Turkey contribute to toxic deaths. Therefore, further reduction of therapy and conditioning with BuMel has been integrated into our ongoing study TPOG-NBL 2009. The preliminary results of the TPOG-NBL 2009 trial indicate that protocol is well-tolerated and EFS at 3 years for arm CCT versus ASCR, respectively, was 33% versus 37% (log-rank $P = 0.02$) and OS at 3 years for arm CCT versus ASCR, respectively, was 53% versus 59% (log-rank $P = 0.43$) (unpublished data). A somewhat improved outcome has been obtained with myeloablative chemotherapy with ASCR after intensive chemotherapy. However, more than one-half of these patients will still recurrence and die to the tumor.[24,25] Minimal residual disease therapy with 13-cis-retinoic acid has been a standard in high-risk neuroblastoma care since the late 1990s. More recent studies all included immunotherapy which demonstrated improved outcome. Immunotherapy targeted against the GD2+ antigen is now being more widely adopted as standard therapy which has been shown to further improve outcome, is not commercially available in Turkey.[26] MIBG treatment is another possible approach to improve outcome.[27]

CONCLUSION

Survival rates of high-risk neuroblastoma have improved over the last decade in Turkey. The main problem in the management of these patients is the effective implementation of the planned therapies with early progression and death. When this study was taking place; myeloablative chemotherapy with ASCR has not augmented the therapeutic end point in our country's circumstances. The adequate supportive care and the higher patients' compliance are attained beside improved minimal residual disease therapy, the better survival rates might be obtained in high-risk neuroblastoma patients received myeloablative chemotherapy and ASCR.

Acknowledgement

The investigators would like to acknowledge the following colleagues who join the study with their patients. Yavuz Koksal, Suna Emir, Ekrem Unal, Gulnur Tokuc, Funda Corapcıoglu, Faik Sarıalioglu, Atilla Tanyeli, Vedat Koseoglu, Aykan Ozguven and Betul Biner.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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