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The Impact of Pretransplant Disease Characteristics on the Outcome of Autologous Stem Cell Transplantation for Neuroblastoma with High-Risk Features: A Retrospective Model from a Limited Resources Country

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Abstract

High-risk neuroblastoma still has poor survival outcome. Improvement of outcome is attributed to the consolidation of chemotherapy by autologous bone marrow transplant. Further improvement of the outcome by tandem autologous transplant is followed by immune therapy. We aimed with this study to correlate initial disease characteristics with the outcome of transplanted high-risk neuroblastoma. A retrospective analysis was done for 73 transplanted patients. Patients were treated in Children's Cancer Hospital Egypt from July 2012 to July 2015. Seventy patients received Busulphan/Melphalan conditioning. The 3-year overall survival (OS) and event-free survival (EFS) was 63.3% and 51.3%, respectively. Disease stage did not impact the OS and EFS, P = 0.54 and 0.62 respectively. Status of MYCN did not reflect statistically on outcome for tumors with amplified compared to nonamplified (EFS, 49% and 63.1%, respectively). Response after induction chemotherapy pointed that patients who had objective response (complete response, very good partial response and partial response) were better compared to those with less response with EFS

and OS of 53.3% and 64.2% compared to 49.3% and 63.5%, respectively, which may indicate that chemo-sensitive tumors have better outcome. By the end of the study, twenty-seven patients relapsed, out of them 25 patients died. Pretransplant risk features for neuroblastoma was nullified by autologous stem cell transplant. The modest outcome observed, highlights some limitations that need to be sorted out in countries with limited resources. The introduction of immune therapy and tandem transplant is needed to achieve a better outcome, yet it adds to more financial burden.

Keywords

Neuroblastoma, Limited-Resource, Autologous Bone Marrow Transplant, Busulphan, Melphalan

1. Introduction

Children with high-risk neuroblastoma have unsatisfactory long-term survival despite intensive multimodal treatment [1]. Conventional chemotherapy therapy can prolong life, most still succumb to progressive disease [2]. Improvement of the outcome in patients with high-risk neuroblastoma is attributed to the consolidation of induction chemotherapy by autologous bone marrow transplant (ABMT) [3] [4] [5]. The use of cis-retinoic acid (cisRA) following myeloablative chemotherapy showed improvement in the three-year event-free survival (EFS) for the group who was randomly assigned to ABMT compared with the arm of chemotherapy alone, although it did not reflect on the overall survival (OS) [6] [7].

Recently, further improvement in outcome has been reported in high-risk neuroblastoma after using immunotherapy (Anti-Ganglioside GD2 antibody) following high dose chemotherapy and tandem ABMT with three years O.S of 61.4% and 48.4% for patients who received a double transplant and single transplant, respectively [8].

Age, disease extent, MYCN gene amplification status, DNA ploidy status, and histopathology are the main prognostic variables affecting the outcome of the disease [9] [10] [11]. Patients with age > 18 months had worse outcome [12]. Other adverse prognostic factors, besides stage IV disease, MYCN gene amplification and unfavorable histopathology, are ferritin level > 143 ng, and an inadequate response to induction chemotherapy [6] [13].

Herein, we report the results of transplanted high-risk neuroblastoma cohort treated at Children's Cancer Hospital Egypt to denote the prognostic significance of disease variable on the survival outcome after ABMT (EFS and OS).

2. Materials and Methods

2.1. Patient and Disease Characteristics

Retrospective data search was done for the clinical data of 540 patients with neuroblastoma treated in our center in the time period from July 2012 to July

2015. Three hundred thirty-one patients (61.2%) were labeled as high-risk neuroblastoma. Autologous stem cell transplantation was performed for 73 patients in the same time period and cases were followed until December 2017. Provided written informed consent is collected before the start of treatment. The study was approved by the institutional review board. Initial disease characteristics including; age, stage, histopathology, MYCN status, different metastatic sites, response to induction chemotherapy and extent of surgical resection were correlated to the survival outcome post-ABMT. All patients were new cases and below 18 years of age at presentation. At the time of transplant patients should have achieved at least partial remission for their initial disease. Patients treated outside our center were excluded. The international neuroblastoma pathology classification (INPC) was used to define the prognostic morphologic features of the tumor and the Children's Oncology Group (COG) criteria were used to stratify the patients' risk [14] [15]. Response to treatment was classified according to international neuroblastoma response criteria (INRG) [16].

2.2. Treatment

All patients received induction chemotherapy according to COG A3973 protocol. Surgery was done post fifth cycle, if operability is possible (either complete resection or debulking operation), or deferral from surgery if the patient achieved very good partial response (VGPR) locally by systemic chemotherapy. The tumor resection was classified as complete resection (95% - 100%), gross total resection (90% - 95%), incomplete resection (50% - 90%), and biopsy (<50%) [17].

Variable number of chemotherapy cycles consists of Vincristine, Carboplatin, Etoposide and Cyclophosphamide (OJEC) that were given as maintenance treatment for patients with good response until ABMT was performed, while patients with less than VGPR or patients who progressed or relapsed prior to transplant were salvaged by receiving Etoposide, Carboplatin, Ifosfamide (ICE) chemotherapy or Topotecan and Cyclophosphamide (Topo/CTX).

After induction chemotherapy, consolidation with autologous bone marrow transplantation was offered for patients with at least partial remission (PR) and with negative bone marrow confirmed with immune histochemistry (IHC) by synaptophysin and chromogranin. Post-ABMT, irradiation to the primary tumor and metastatic sites is offered and followed by cisRA for a total of 12 months. The main conditioning regimen was Busulphan/Melphalan (Bu-Mel) in 70 patients and three other patients received CEM (Carboplatin, Etoposide, Melphalan).

2.3. Statistical Analysis

Statistical analysis was done using IBM© SPSS© Statistics version 22. Numerical data were expressed as median and range. Qualitative data were expressed as frequency and percentage. Survival analysis was done using the Kaplan-Meier method and comparison between two survival curves was done using the log-rank test.

All tests were two-tailed. A p-value < 0.05 was considered significant. Event-free survival (EFS): It was measured from the date of diagnosis to the date of progression or relapse or death. Overall survival (OS): It was calculated from the date of diagnosis till the date of death or date of last follow-up.

3. Results

Patient and disease characteristics are summarized in Table 1. The median age for patients was 3 years (range 1 - 7 years). Seventy-three patients were included with slight male predominance (M:F = 1.3:1). Nineteen cases were stage III and 54 patients were stage IV.

Table 1. Patient and disease characteristics for transplanted high-risk neuroblastoma.

Variables	Total number (n = 73)	Percentage (%)
Age median years (range)	3 years (range 1 - 7 years)	
Sex		
Male	42	57.5%
Female	31	42.5%
Primary site		
Adrenal	65	89.0%
Abdominal (non-adrenal)	5	6.8%
Mediastinum	2	2.7%
Neck	1	1.3%
Stage (INSS)		
Stage 3	19	26.0%
Stage 4	54	74.0%
Pathology		
NB	69	94.5%
GNB	3	4.0%
Not done	1	1.5%
INPC		
Favorable	70	96.0%
Not available	3	4.0%
NMYC		
Amplified	21	28.7%
Non-amplified	50	68.4%
Unknown	2	2.9%
Bone marrow infiltration		
No	28	38.3%
Yes	43	58.9%
Not done	2	
Bone metastasis (bone scan)		
No	30	41.0%
Yes	39	53.4%
Not done	4	5.4%
Distant lymph node involvement		
No	19	26.0%
Yes	54	73.9%

Continued

Brain metastasis		
No	67	91.7%
Yes	6	8.2%
Liver metastasis		
No	69	94.5%
Yes	4	5.4%
Extent of surgical resection		
Complete resection	24	32.8%
Gross total resection	5	6.8%
Incomplete resection	10	13.6%
Biopsy	4	5.4%
No surgical intervention	30	41%
Disease response post-induction high-risk protocol		
CR	8	10.9%
VGPR	32	43.8%
PR	23	31.5%
Less than PR	10	13.6%
Disease status at the time of transplant		
CR	11	15.0%
VGPR	51	69.8%
PR	9	12.3%
Less than PR	2	2.7%
Relapse mortality	18	24.6%
Non-relapse related mortality	7	
Diffuse alveolar hemorrhage	3	
Septic shock	2	9.5%
Hepaticveno-occlusive disease	1	
Therapy-related myeloid neoplasm	1	

INNS: international neuroblastoma staging system, INPC: international neuroblastoma pathology classification, NB: Neuroblastoma, GNB: Ganglioneuroblastoma, CR: complete remission, VGPR: very good partial remission, PR: partial remission

Table 2 summarizes the correlation of different prognostic factors with transplant outcome. Seventy patients received Busulphan/Melphalan conditioning regimen, while CEM regimen was given to three patients. The 3-year OS and EFS for the whole cohort were 63.3% and 51.3%, respectively (Figure 1 and Figure 2). For 3-year survival, the initial disease stage did not show statistical significance on the overall and event-free survival, $P = 0.54$, and 0.62 respectively. Status of MYCN also did not impact survival outcome for those with amplified compared to no amplification (EFS and OS; 49%, 51.1% and 52.6%, 63.1%, respectively). The response post induction chemotherapy did not show statistical significance. The latter factor, showed that patients who had objective response either with complete response (CR), very good partial response (VGPR) or partial response (PR) had a marginal better outcome compared to those with less than PR with EFS and OS of 53.3% and 64.2% compared to 49.3% and 63.5%, respectively ($P = 0.45$ and 0.75), which may indicate that better transplant outcome could be

Table 2. Correlation for different prognostic factors with Overall (OS) and event-free survival (EFS).

	OS at 36 months	P-value	EFS at 36 months	P-value
Study patients (n = 73)	63.3%		51.3%	
Age (years)				
< 1.5	66.7%		66.6%	
≥ 1.5 < 5	58.7%	0.31	46.7%	0.49
≥ 5	73.8%		66.2%	
Stage				
III	68.1%	0.54	52.6%	0.626
IV	62.7%		51.0%	
MYCN status				
Amplified	51.1%		49.0%	
Not amplified	63.1%	0.428	52.6%	0.96
Unknown	100%		50.0%	
Bone marrow infiltration				
No	70.7%		58.9%	
Yes	59.3%	0.15	46.8%	0.15
Unknown	100%		0%	
Bone metastasis				
No	62.2%		56.1%	
Yes	63.5%	0.402	44.4%	0.09%
Unknown	100%		100%	
Brain metastasis				
No	69.4%	0.425	48.7%	0.211
Yes	83.3%		83.3%	
Liver metastasis				
No	64.5%	0.236	51.9%	0.499
Yes	33.3%		33.3%	
Distant lymph node involvement				
No	68.1%	0.08	55.1%	0.44
Yes	61.6%		50.1%	
Post-induction CTh response				
CR/VGPR/PR	64.2%	0.75	53.3%	0.45
Less than PR	63.5%		49.3	
Extent of surgical resection				
Complete resection	50.5%		42.7%	
Less than complete resection	56.3%	0.4	41.7	0.44
No surgical intervention	75.1%		63.7%	
Disease status at time of transplant				
CR/VGPR/PR	60.7%	0.34	50.1%	0.54
<PR	81.8%		60.6%	

Abbreviations: CR: complete remission, VGPR: very good partial remission, PR: partial remission.
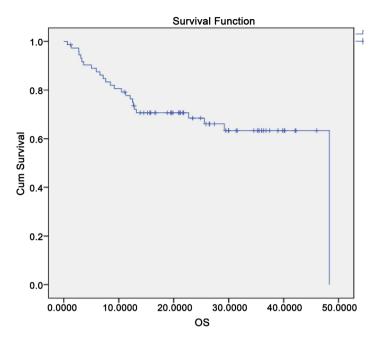
Figure 1. The 3-year overall survival for transplanted high-risk neuroblastoma.
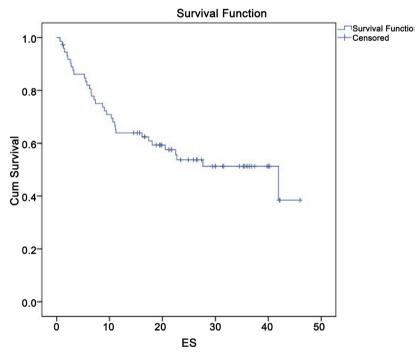

Figure 2. The 3-year event-free survival for transplanted high-risk neuroblastoma.

achieved, when the disease has more chemo-sensitivity, but the sample size included was small to show statistical significance. In addition, the disease status pre-transplant did not show a statistically significant impact on either the OS or EFS (Table 2).

For the whole cohort, 24 (32.8%) patients underwent complete surgical resection of their tumor at the time of local control; gross total resection and incomplete resection was achieved in 5 (6.8%) and 10 (13.6%) patients, respectively.

Surgery was not feasible in 34 (45.9%) cases, were biopsy was performed in 4 (5.4%) patients. Statistical significance was not observed in relation to the extent of surgical resection and the outcome post-transplant with p-value of 0.44 for EFS and 0.4 for OS.

Maintenance chemotherapy OJEC (Vincristine, Carboplatin, Etoposide, and Cyclophosphamide) was given for 40 patients who achieved CR or VGPR to avoid disease progression due to the long transplant waiting list, with 3 years EFS and OS of 55.6% and 64.6%, respectively. Thirty-three patients received salvage therapy either with ICE regimen (Ifosfamide, Carboplatin, and Etoposide) or TOPO/CYCLO regimen (Topotecan and Cyclophosphamide) due to inadequate response (less than VGPR) or progressive disease post-induction therapy with lower 3 years EFS and OS of 45.7% and 58.9%, respectively. Insignificant survival difference was observed between the maintenance and salvage groups, p = 0.24 for both OS and EFS.

By the end of the study, 27 (36.9%) patients relapsed post-transplant, out of them 25 patients died. Transplant-related mortality in the first 100 days was 8.2% (6 patients), while disease progression was the main cause of death in 18 patients (Table 1).

4. Discussion

Risk-stratification of neuroblastoma is the standard for optimal treatment. The Children's Oncology Group (COG) has used different factors to stratify patient risk [9]. Progress has been made in improving the outcome of neuroblastoma reaching 10-year OS rates of 65% - 75%, the outcome of the high-risk group is still unsatisfactory [18] [19]. High dose chemotherapy and ABMT is considered the standard therapeutic regimen in high-risk patients with marginal survival improvement compared to conventional chemotherapy [1]. Recently, further improvement has been made with the introduction of tandem ABMT and immune therapy [20], but these are costly procedures which can't be afforded in countries with limited resources. In our center, we are still adopting the consolidation by single autologous transplant after achieving CR, VGPR, PR or stable biologically inactive residual followed by local radiation, and cis-retinoic acid.

The current study aimed to analyze different prognostic factors which may have an impact on the survival outcome post-transplant. It is generally agreed that older age, unfavorable histology, advanced stage, and MYC-N gene amplification are associated with poor outcome [9]. Others also proved that stage 4 disease, MYCN gene amplification, unfavorable histopathology, and less than VGPR to induction chemotherapy were associated with low EFS as well as OS (P.0232) [6]. Another study showed that the main prognostic factors that resulted in lower EFS and OS post-transplant were the remission status at the time of auto-SCT (OS; p = 0.04) and unfavorable histology [13].

Unlike our study, due to the small number of patients, different patient and disease characteristics did not appear to have statistical significance on the

transplant outcome. Still, we can observe a tendency towards lower 3-year EFS and OS in patients with less than PR (8 cases) compared to those who had better chemo-response after induction treatment. This points out that in this study, if a sufficient number of patients were distributed across the groups according to their treatment response a better significant result would have appeared.

International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) study concluded that OS is better with Bu-Mel conditioning regimen compared to CEM (60% vs. 48%, respectively) [21]. We also reported in a previous study, more hepatic (p = 0.04) and renal toxicities (p = 0.004) in patients transplanted using CEM than Bu-Mel in the first 100 days post-ABMT [22]. Worth noting that all patients included in this study received Bu-Mel except for three patients who received CEM, all died with transplant-related mortalities, and despite the unequal distribution between the 2 groups but Bu-Mel conditioning was associated with higher EFS (53.5%;) and OS (66.1%) compared with those who received CEM with p = 0.01 and p = 0.001, respectively.

The 3-year survival rates in this study were 51.3% for EFS and 63.3% for OS with 25 cases died out of disease progression and other causes. Lower survival rates were reported by others, with patients' groups distributed equally between Bu-Mel and CEM, reporting 3-year EFS and OS of 31% and 51.7%, respectively [13]. The higher OS and EFS may be attributed to the unified Bu-Mel conditioning used in our transplant center.

When comparing the current results with another study previously done in our hospital, Mousa *et al.* reported 4-year OS and EFS for transplanted high-risk neuroblastoma of 42.7% and 35.6%, respectively [23]. The explanation for this may be related to the more intensified induction in COG A3973 protocol used by our center starting from 2012 compared to the less intensified SFOB protocol used before 2012, which highlights the importance of induction response on the transplant outcome.

The limitations of this study are being a single center with a retrospective design and average sample size, but it describes the transplant experience from a region with limited resources for a frequent pediatric cancer.

5. Conclusion

The impact of pretransplant risk features on the outcome of high-risk neuroblastoma was nullified by autologous stem cell transplant; however, response to induction chemotherapy seems to have an impact on the outcome of transplant. The modest outcome observed in this study, highlights many challenges that need to be sorted out in countries with limited resources. The introduction of new immune therapy, as well as tandem transplant, is needed to achieve a better outcome, yet it adds to more financial burden in developing countries.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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