Clinical Characteristics and Outcome of High Risk Neuroblastoma Treated at Sohag Cancer Center, Egypt

Sayed HA[1], Morsy MA[1], Nagib MG[2]

[1] Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[2] Pediatric Oncology Department, Sohag Cancer Center, Sohag, Egypt

Abstract:

Background objectives: Neuroblastoma is the most common extracranial solid tumor in children. Nearly half of them are high risk at diagnosis according to the International Neuroblastoma Risk Group Staging System (IRGSS). Patients with high risk tumors have dismal outcome with 5 years survival rate only 50% despite aggressive therapy. The study aimed to present the clinical characteristics and outcome in patients diagnosed with high risk neuroblastoma (HR-NB) during the period from January 1st, 2014, to December 31st, 2019 and their follow up data were collected till 30th June 2020.

Methods: A retrospective study was conducted on a group of 34 patients diagnosed with HR-NB and treated at Sohag Cancer Center by two different chemotherapy protocols.

Results: The study group had a median age of 33 months, with 16 patients (47%) being males and 18 patients (52.9%) females. Most of patients (79.4%) aged ≥1.5 years. The main presenting symptoms included abdominal mass (88%), pallor (47%) and abdominal pain (45.2%). All patients presented with advanced-disease stage, with 91.1% had stage IV and 8.8% had stage III. Abdomen was the most common primary site for the disease reported in 88.2%. Nineteen patients treated according to the OPEC/OJEC protocol (55.9%) (group 1) and fifteen patients received the High risk COG protocol (group 2). Local control by surgery was feasible in 22 patients. At a median follow up of 29 months, the 3-year OS and EFS were 47 % and 35.3% respectively which were significantly affected by MYC N gene status, protocol of chemotherapy used, receiving radiotherapy and having ABMT. Myelosuppression was the main treatment related toxicity reported in all patients.

Conclusion: The study's findings align with similar research on HR-NB treatment considering very poor prognosis of patients with HR-NB. Using less aggressive treatment protocol as with OPEC/OJEC showed better survival and less morbidity among patients in this study. Also, MYC N gene status, receiving radiotherapy and having ABMT were significantly affecting disease outcome and survival of patients with HR-NB.

Keywords: High risk Neuroblastoma, Outcome, Treatment morbidities.

Received: 28 March 2024
Accepted: 16 April 2024

Authors Information:
Heba Abdel-Razik Sayed
Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
email: hebadina2007@yahoo.com

Mohammed Ahmed Morsy
Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
email: ahmedmohammed7829@gmail.com

Mariam Girgis Nagib
Pediatric Oncology Department, Sohag Cancer Center, Sohag, Egypt
email: mariamgirgis20@gmail.com

Corresponding Author:
Mariam Girgis Nagib
Pediatric Oncology Department, Sohag Cancer Center, Sohag, Egypt
email: mariamgirgis20@gmail.com

Introduction:

Neuroblastoma is the most common extracranial solid tumor in children, accounting for 8% to 10% of all childhood cancers, half of them had High risk Neuroblastoma (HR-NB). Almost 90% of neuroblastomas occur in children < 5 years of age with a median age at diagnosis of about 19 months. It arises from neural crest cells that can occur at any point along the sympathetic ganglia or the adrenal medulla, most primary tumors occur within the abdomen (65%), other sites include cervical, thoracic and paraspinal tumors [1, 2]. Neuroblastoma is composed of three histologic patterns based on the degree of tumor cell differentiation: neuroblastoma, ganglioneuroblastoma and ganglioneuroma [3].

Patients are classified into low, intermediate and high-risk according to the INRGSS in which, high-risk patients are those who have MYCN amplification, In addition, any patient with metastatic disease age 18 months or older is considered high risk irrespective of MYCN. Patients with high risk tumors have dismal outcome with 5 years survival rate of around 50% despite aggressive therapy [4, 5, 6].

The aim of this work is to study the pattern and outcome of HR-NB patients treated at the Pediatric Oncology Department of Sohag Cancer Center (SCC), Egypt.

Materials and Methods:

This retrospective analytic study conducted at the Pediatric Oncology Department, spanning from January 1st, 2014, to December 31st, 2019. The study included pediatric patients diagnosed with high risk Neuroblastoma. Ethical considerations were rigorously adhered to, with approval obtained from the Institutional Ethical Committee in South Egypt Cancer Institute (SECI), Assiut University and in Sohag Cancer Center.

The inclusion criteria encompassed boys and girls under the age of 18 years, bearing histologically verified neuroblastoma diagnosis according to International Neuroblastoma Pathology classification system with presence of the high risk criteria according to International Neuroblastoma Staging system (INSS) [7]. Importantly, included patients were those newly diagnosed with HR-NB, excluding any individuals with prior chemotherapy and/or radiotherapy history and patients with low or intermediate risk NB.

Data Collection

Patient data was meticulously gathered from medical records, encompassing the following:

Demographic data, presenting symptoms & signs, site of primary & metastatic disease, initial LDH level, pathology, MYC N amplification and disease stage and stratifications according to INSS [7].

According to treatment received, patients were grouped into 2 groups: Group1: included patients admitted between January 2014 up to January 2017 who were treated according to POG protocol which consists of 6 courses of OPEC alternating with OJEC [8]. Each cycle administered every 3 weeks for a total of 12 cycles and Group2: included all patients admitted from February 2017 up to December 2019 who were treated according to HR- NB COG protocol which consists of 6 cycles, one cycle every 3 weeks [9].

Data related to treatment response according to International Neuroblastoma Response Classification, morbidity according to CTCAE and outcome were also collected. [10,11]

Statistical analysis

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. As the data were not normally distributed, so quantitative data were statistically described in terms of mean ± SD and median and range. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using Kruskal Wallis test or Mann Whitney U test because the data were not normally distributed. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Overall Survival (OS) calculated from date of diagnosis to last date of follow up or date of death for any cause and Event free survival (EFS) calculated from date of diagnosis to date of first treatment failure of any kind as relapse, absence, death, major treatment toxicity that required cessation of chemotherapy were estimated with Kaplan-Meier method and differences were assessed by the log-rank test. Cox regression was calculated to determine significant factors associated with mortality. P-value is always 2 tailed set significant at 0.05 levels.

Results:

This study included 34 patients who were diagnosed and treated as HR-NB during the period from January 1st, 2014, to December 31st, 2019. The Median age of the studied patients was 33 months ranged between 4 to 76 months. Most patients (79.4%) aged ≥ 1.5 years with slight female predominance (52.9%), male to female ratio was 1:1.1.

The main presenting symptoms were abdominal mass in 30 patients (88.2%), followed by pallor in 16 patients (47.1%) and abdominal pain in 14 patients (45.2%). The majority of patients presented by stage 4 (91.1%) and 3 patients (8.8%) with stage 3.

Imaging studies diagnosed abdomen as the primary site in most of cases (88.2%), 3 patients presented by mass in paraspinal region (8.8%) and the remaining one presented by mediastinal mass (2.9%). Bone marrow infiltration in 21 patients (61.7%) followed by bone metastasis seen in 20 patients (58.8%).

Histopathologically, 88.2% of cases had unfavorable neuroblastoma histopathology and most had undifferentiated histopathology (73.5%).

Nearly one fourth of the patients had LDH level ≥ 1500 U/L at presentation. MYC N gene studying was applicable only in 9 cases, gene amplification was reported in 6 cases (66.6%) of them. Nearly one fourth of the patients had LDH level ≥ 1500 U/L at presentation. Table 1 shows all criteria of the study group at presentation.

Treatment:

Group 1:

included 19 patients who received the OPEC/ OJEC protocol (55.9%) during the period from January 2014 to January 2017: one patient lost follow up very early after receiving 1st dose of chemotherapy, the 18 patients were evaluated after receiving 3 courses of OPEC/ OJEC. Their response assessment revealed that: 13 patients (72.2%) had partial response (PR), 3 patients (16.6%) had stable disease (SD) and 2 patients (11.11%) had disease progression (PD). Local control by surgery was feasible in 14 /18 patients (77.77%). Regarding radiotherapy, three patients (16.6%) received curative doses of RTH on residual tumor after surgery, four patients (22.22%) received RTH post ABMT and 3 cases received palliative radiotherapy.

Table (1): Clinicopathologic criteria of the study group.

Variable name	N (34 patients)	(%)
➢ **Age** (months), Median (range)	33 (3-144)	
➢ **Age groups**:		
< 1.5 years	7	(20.6)
≥ 1.5 years	27	(79.4)
➢ **Sex**:		
Male	16	(47.1)
Female	18	(52.9)
Males: Females 1:1.1		
➢ **Primary site of the tumor**:	17	(50)
Retroperitoneal	13	(38.2)
Suprarenal	3	(8.8)
Paraspinal	1	(2.9)
Mediastinal		
➢ **Metastasis**:		
Yes	31	(91.1%)
No	3	(8.8%)
➢ **Site of metastasis**:		
Bone metastasis	20	(58.8)
BM metastasis	21	(61.7)
LN metastasis	14	(41.1)
Liver metastasis	6	(17.6)
➢ **Stage:**		
Stage 3	3	(8.8)
Stage 4	31	(91.1)
➢ **Histology:**		
Unfavorable	30	(88.2)
Favorable	4	(11.8)
➢ **Differentiation:**		
Well differentiated	1	(2.9)
Poorly differentiated	8	(23.5)
Undifferentiated	25	(73.5)
➢ **MYC N gene*:**		
Amplified	6	(66.6)
Not amplified	3	(33.3)
➢ **LDH:**		
< 1500	25	(73.5)
≥ 1500	9	(26.5)

* Done in 9 patients only.

Group 2:

included 15 patients who received the High risk COG protocol from February 2017 to December 2019. Response assessment was done after cycle 5 (before surgery) and showed that: 9 patients (60%) achieved PR, 4 patients (26.6%) achieved VGPR and 2 patients (13.3%) had PD. Eight patients (53.3%) were operable: six of them (40%) had complete local excision, one case (6.6%) had >90 % local excision. Two patients (13.33%) received curative radiotherapy on residual tumor after surgery, 5 patients (33.33) received radiotherapy post ABMT and 3 patients received palliative radiotherapy.

Ten patients underwent ABMT, 5 patients in each group after achieving CR (6 patients), VGPR (3 patients) and PR (one patient) with remission in BM.

Regarding morbidities, myelo-suppression in form of neutropenia and anemia was the main morbidity reported in all patients with (82.3%) of them developed grade 3 neutropenia and (17.6%) developed grade 4 neutropenia. The most common infectious complication was bacterial chest infections reported in 17 patients (50%) followed by fungal chest infections reported in 5 (14.7%) patients. Eleven patients (32.3%) developed grade 3 anemia and 5 patients (11.7%) developed grade 4 anemia. Mucositis was the second most common treatment related toxicity reported in 80 % of patients with 7 patients (20.5%) developed advanced grades of Mucositis (grade 3& 4). Hepatotoxicity grade II-III was reported in 7 (20.5%) patients either chemotherapy induced or Hepatitis virus infection reactivation.

At a median follow up of 29 months, half of the patients were living, 47% died and one patient lost follow up. Disease progression was the main cause of death among the study group either during 1st line therapy (7 patients) or after relapse (6 patients). Treatment related toxicity in form of grade 4 neutropenia with sepsis was the cause of death in 3 patients during 2nd line chemotherapy.

Relapse reported in 9 patients (27%) within a median time of 3 months (range 1-9 months). Bone was the main site of relapse in most of patients (80%). Eight patients of them were treated by 2nd line chemotherapy with PD reported in 6 patients while one patient achieved CR and the remaining one achieved PR with one patient had relapse post AMBT and received palliative chemotherapy and palliative radiotherapy.

The 3-year overall survival (OS) was 47% and event free survival (EFS) was 35.3%. Figures (1,2).

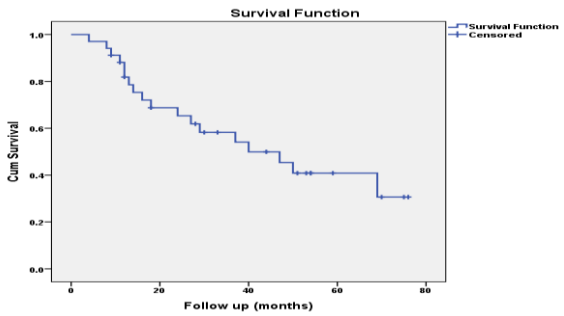

Figure 1. Three-year overall survival of the study group

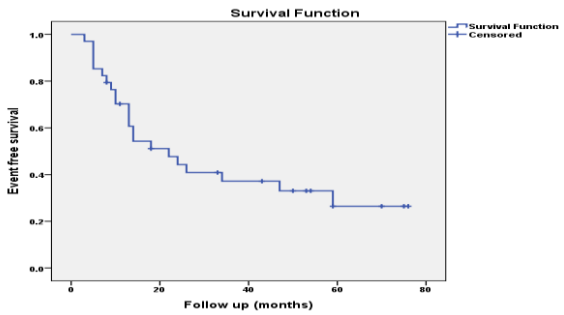

Figure 2. Three-year event free survival of the study group

Several factors were found to significantly affect OS with worse outcome associated with MYC N amplification (3-year OS 0±00% VS 100% for those with MYC N positive and negative respectively, P=0.024) and better outcome for those receiving curative radiotherapy and in patients who had ABMT (P= 0.001 & P=0.033 respectively). The chemotherapy protocol used was near significant in affecting OS (3-year OS was 68.4 ± 10.7% VS 39.1 ± 15.8% for patients treated by OPEC/OJEC protocol versus HR COG protocol respectively (P=0.056).

As regard Event free survival, several factors significantly affected it with worse outcome associated with MYC N gene amplification (P=0.009); and better outcome for those receiving induction chemotherapy according to OPEC/OJEC protocol (P=0.018), receiving curative radiotherapy (P=0.008) and who had ABMT (P=0.022). Table (2), figure (3-10).

Table (2): Prognostic factors affecting OS & EFS of studied patients.

Variable	OS (3-years)		EFS (3-year)	
	Estimate ± SE	P value	Estimate ± SE	P value
➢ Age:				
<1.5 years	40.0 ± 21.9%	0.582	40.0 ± 21.9%	0.934
≥1.5 years	61.5 ± 9.7%		36.7 ± 9.5%	
➢ Sex:				
Male	47.6 ± 13.9%	0.192	38.7 ± 13.1%	0.337
Female	65.8 ± 11.4%		35.6 ± 11.9%	
➢ Site:				
Retroperitoneal	65.5 ±12.6%	0.072	52.8 ± 13.2%	
Suprarenal	35.2 ±13.9%		15.4 ± 10.0%	0. 180
Paraspinal	00		66.7 ± 27.2%	
Mediastinal	00		0.0 ±0.0%	
➢ Disease stage:		0.190		
Stage 3	100.0 ± 0.0%		100.0 ± 0.0%	0.127
Stage 4	55.3 ± 9.4%		32.7 ± 8.8%	
➢ Pathology:	56.1 ± 9.6%		36.2 ± 9.2%	
Unfavorable histology		0.506		0.590
Favorable histology	75.0 ± 21.7%		37.5 ± 28.6%	
➢ MYC N:				
Amplified	0.0 ±0.0%	**0.024**	0.0 ±0.0%	**0.009**
Not amplified	100.0 ± 0.0%		100.0 ± 0.0%	
➢ LDH:				
< 1500	52.1 ± 10.6%	0.575	41.7 ± 10.2%	0.975
≥ 1500	76.2 ± 14.8%		25.4 ± 15.5%	
➢ Chemotherapy protocol:				
OPEC/OJEC Protocol	68.4 ± 10.7%	**0.056**	52.6 ± 11.5%	**0.018**
High risk COG protocol	39.1 ± 15.8%		0.0 ± 0.0%	
➢ Surgery:		0.461		
Complete excision	53.1 ± 14.1%		35.9 ± 12.8%	
Excision of >90%	------		----	0.417
Partial excision	80.0 ± 17.9%		53.3 ±24.8%	
No surgery	50.0 ± 14.4%		25.0 ± 12.5%	
➢ Radiotherapy:				
Yes	79.5 ± 13.1%	**0.001**	59.6 ± 14.1%	**0.008**
No	36.6 ± 11.3%		22.0 ± 9.6%	
➢ BM transplantation:				
Yes	90.0 ± 9.5%	**0.033**	56.3 ± 16.5%	**0.022**
No	44.2 ±11.5%		30.3 ±16.5%	

OS; overall survival, EFS; event free survival, LDH; lactate dehydrogenase enzyme COG; children oncology group, BM; bone marrow.

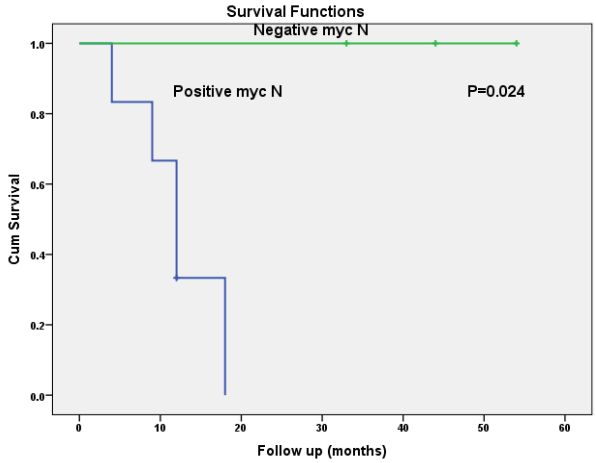

Figure 3. Three-year overall survival of the study patients according to the MYC N gene amplification.

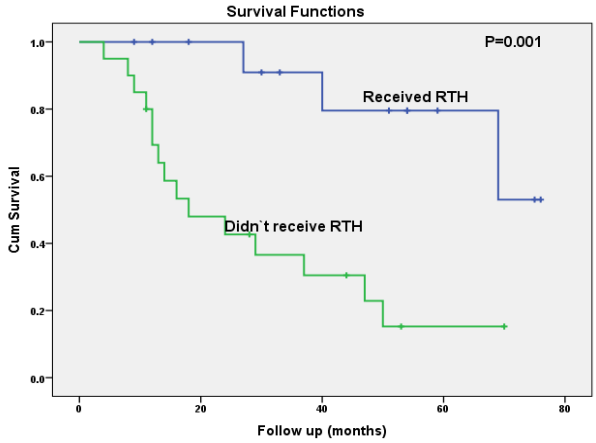

Figure 4. Three-year overall survival of the study group according to receiving curative radiotherapy.

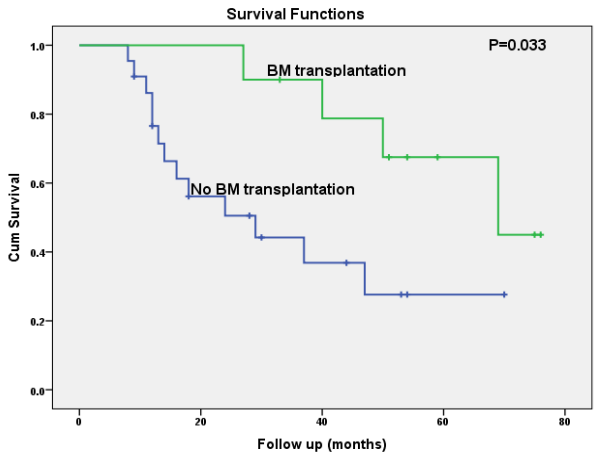

Figure 5. Three-year overall survival of the study group according to autologous bone marrow transplantation.

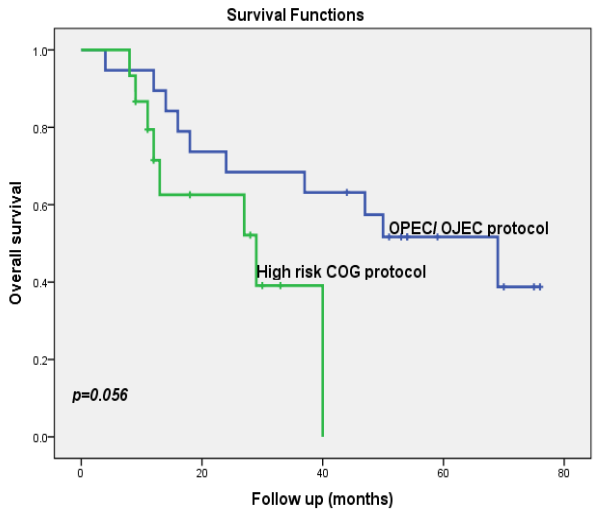

Figure 6. Three-year overall survival of the study group according to the type of chemotherapy regimen received.

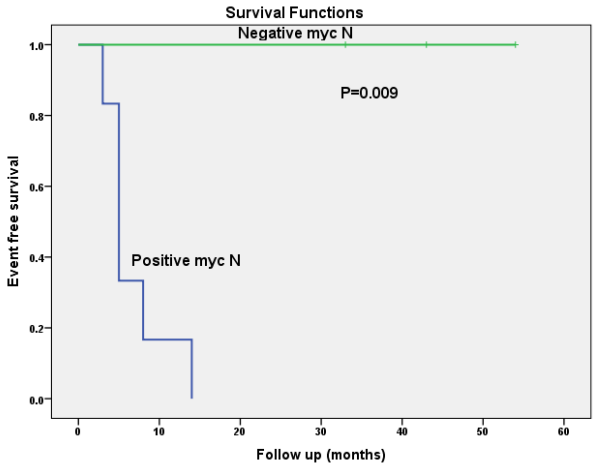

Figure 7. Three-year event free survival of the study group according to the MYC N amplification.

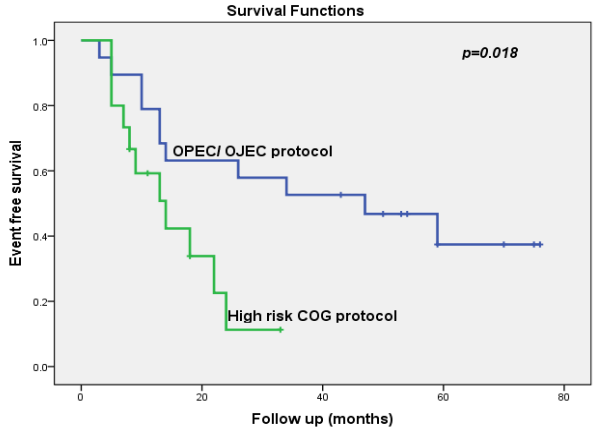

Figure 8. Three -year event free survival of the study group according to the type of chemotherapy regimen received.

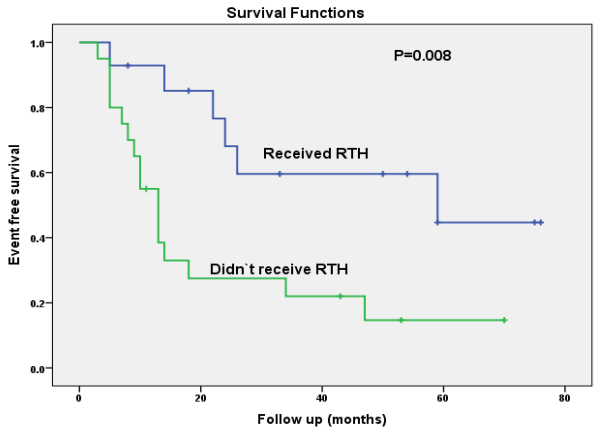

Figure 9. Three-year event free survival of the study group according to receiving curative radiotherapy.

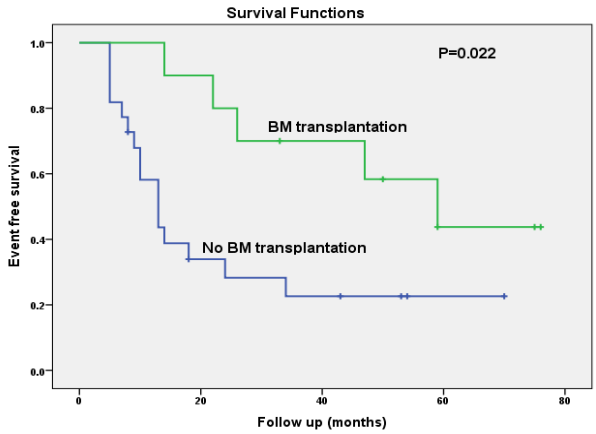

Figure 10. Three-year event free survival of the study group according to the receiving autologous bone marrow transplantation.

Discussion:

This study presents the results of a retrospective study included 34 HR-NB patients treated at Sohag Cancer Center. The median age at diagnosis was 33 months, which is similar to (Moussa et al., 2013) study [12] and was younger than what was reported in (Suwannaying et al., 2022) study with median age of 36 months ranging from 8 months to 18 years [13]. In this study, most of patients (79.4%) aged ≥ 1.5 years, this is similar to (Moussa et al., 2013) and (El-Sayed et al., 2010) studies as most of their patients aged > 1 year of age at time of diagnosis [12,14]. We reported slight female predominance with males to females ratio 1:1.1. this contrasts with male predominance reported in (Moussa et al., 2013), (Brodeur et al., 2016) and (Kletzel et al., 2002) studies [12, 10, 15]. Most patients presented by abdominal mass (88.2%), pallor (47.1%) and abdominal pain (45.2%) which is constant with (Moussa et al., 2013) study that reported abdominal mass was the main presentation [12] Chu et al., 2011 in their study reported swellings in head and neck region in most of their patients [16].

In this study, most cases presented by abdominal tumors (88.2%) with only 3 cases had tumors located in the paraspinal region (8.8%) and one case had mediastinal NB, this is constant with several studies that reported abdomen as the most common site of tumor in their patients [12,15,17]. Bone marrow was the most common site of metastasis in this study reported in 61.7% of patients followed by bone metastasis reported in 58.8% of patients. Moussa et al. and El-Sayed et al. studies reported similar results [12,14], in contrasts Lee et al. reported bone metastases as the most common site of metastasis reported in 80 % of their patients followed by BM metastases (67.4%) [17].

Majority of our cases had unfavorable histology (88.2%) and undifferentiated histopathology (73.5%). This is in consistence with several studies that revealed predominance of unfavorable and undifferentiated histopathology in their patients [12,15,17].

MYC N amplification is associated with more aggressive clinical features at diagnosis and a better early response, but a higher progression rate during induction treatment and lower survival rates after relapse/progression [17]. MYC N gene was applicable in 9 patients only and was found to be amplified in 6 of them (66.66%), this is different from (El-Sayed et al. and Lee et al. studies with majority of cases had non amplified MYC N gene (62%, 69.4% respectively) [14,17].

From 2014- 2017, we were treating our patients using OPEC/ OJEC protocol (Group 1) then after that we shifted to HR COG protocol (Group 2). Assessment of treatment response showed that 72.2% of patients had response to treatment in form of achieving PR in Group 1 while in Group 2, good response seen in 86.6% of patients (60% achieved PR, 26.6% VGPR). In contrast to response to chemotherapy, surgical excision was feasible in 77.7% of patients in Group 1 while only 53% of patients in Group 2 were operable. Compared to El-Sayed et al. who used treatment protocol similar to that used in Group 1 in nearby center and Moussa et al. who treated their patients by protocol similar to that used in Group 2. Our results showed much high response to treatment protocols used in both groups [14,12].

Following induction therapy and aiming to eliminate remaining minimal disease, consolidating patients with high dose chemotherapy followed by ASCT and radiation therapy is planed [15]. Ten patients (30.3%) in this study underwent HSCT, this is near to those who underwent HSCT in Moussa et al. study (34.6%) [12].

Historically, around 50 % high-risk neuroblastoma patients have had long-term survival probabilities of less than 15%. With the advent of comprehensive treatment approaches, overall survival rates have improved to around 50% [9]. The 3-year OS & EFS for all patients were 47% and 35.3 % respectively. This is considered high compared to El-Sayed et al. study with the 3-year OS and EFS of HR-NB patients were 20.7% and 6.1% respectively. Also considered high compared to Moussa et al. study (the 4 years OS for the entire HR-NB study patients was 33.7% and EFS of 23.3%) [14,12]. This can be explained by the recent time of the

study period with more update in treatment and supportive care, also availability of ABMT as a tool of treatment.

MYC N amplification, chemotherapy protocol received, radiotherapy and ABMT are the factors found to significantly affect survival outcome in this study with a worse outcome reported for those with MYC N amplification. This supports the adverse effect of amplified MYC N [17] even with the small sample size in this study. Similarly, El-Sayed et al. in a previous study at South Egypt Cancer Institute reported an EFS of 0% in those with amplified versus 37.2% in non-amplified MYC N. Another study in Children`s Cancer hospital, Egyptian 2013 also showed a significant effect of MYC N gene amplification on survival of their patients (p=0.00) [14,2]. Chemotherapy protocol received was another significant factor that affected the survival outcome (OS & EFS) with worse outcome reported with chemotherapy used in HR COG. This can be explained by its high aggressiveness that was associated with high morbidity and mortality.

Conclusion:

In this study, the incidence and outcome of pediatric high risk Neuroblastoma are nearly similar to that reported in the literature. Using less aggressive treatment protocol as with OPEC/OJEC showed better survival and less morbidity among patients in this study. Disease progression was the main cause of death among our patients. MYC N gene status, protocol of chemotherapy used, receiving radiotherapy and having ABMT were significantly affecting the disease outcome and survival of patients with high risk neuroblastoma in this study.

List of Abbreviations

ABMT: Autologous bone marrow transplantation
BM: Bone marrow
CR: Complete remission
DP: Disease progression
EFS: Event free survival
HR COG: High risk Children Oncology Group
HR-NB: High risk Neuroblastoma
HSCT: Hematopoietic stem cell transplant
INSS: International Neuroblastoma Staging System
LDH: Lactate dehydrogenase enzyme
NB: Neuroblastoma
OS: Overall survival
PR: Partial response
SCC: Sohag Cancer Center

References:

1. Lai HA, Sharp SE, Bhatia A, et al. Imaging of pediatric neuroblastoma: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper 2022. Pediatr Blood Cancer. 2023 Jun;70 Suppl 4(Suppl 4):e29974.
2. Maris JM. Recent advances in neuroblastoma. N Engl J Med. 2010 Jun 10;362(23):2202-11.
3. Lanzkowsky P, et al. (honoris causa). In: Manual of Pediatric Hematology and Oncology. 2011 (Fifth Edition).
4. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009, Jan 10. 27(2):289-97.
5. Heck JE, Ritz B, Hung RJ, et al. The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol. 2009 ; 23:125–143.
6. Pinto NR, Applebaum MA, Volchenboum SL,, et al. Advances in risk classification and treatment strategies for neuroblastoma. J Clin Oncol. 2015; 30; 3008-3017.
7. Sokol E, Desai AV. The Evolution of Risk Classification for Neuroblastoma. Children (Basel). 2019 Feb 11;6(2):27. Children (Basel). 2019 Feb 11;6(2):27.
8. Tweddle DA, Pinkerton CR, Lewis IJ, et al. OPEC/OJEC for stage 4 neuroblastoma in children over 1 year of age. Med Pediatr Oncol. 2001 Jan;36(1):239-42.
9. Smith V, Foster J. High-Risk Neuroblastoma Treatment Review. Children (Basel). 2018 Aug 28;5(9):114.
10. 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 Aug;11(8):1466-77.
11.Common Terminology Criteria for Adverse Events (CTCAE) v5.0, (2017): (https://www. www.uptodate.com).
12. Moussa E, Fawzy M, Younis A, et al. Combined Treatment Strategy and Outcome of High Risk Neuroblastoma: Experience of the Children's Cancer Hospital-Egypt. Journal of Cancer Therapy 2013;04(09):1435-1442.
13. Suwannaying k, Techavichit P, Komvilaisak P. et al. Treatment outcomes of high-dose chemotherapy plus stem cell rescue in high-risk neuroblastoma patients in Thailand. Clin Exp Pediatr. 2022 Sep;65(9):453-458.
14. El-Sayed M, Ali M, Sayed H et al. Treatment results and prognostic factors of pediatric neuroblastoma: A retrospective study. Int Arch Med. 2010 Dec 24;3:37.
15. Kletzel M, Katzenstein HM, Haut PR, et al. Treatment of High-Risk Neuroblastoma With Triple-Tandem High Dose Therapy and Stem-Cell Rescue:2002. Results of the Chicago Pilot II Study. J Clin Oncol. 2002 May 1;20(9):2284-92.
16. Chu CM, Rasalkar DD, Hu YJ, et al. Clinical presentations and imaging findings of neuroblastoma beyond abdominal mass and a review of imaging algorithm. Br J Radiol. 2011 Jan;84(997):81-91.
17. Lee JW, Son MH, Cho HW, et al. Clinical significance of MYCN amplification in patients with high-risk neuroblastoma. Pediatr Blood Cancer. 2018 Oct;65(10):e27257.