Prognosis, Survival and Management of Pediatric Patients With Neuroblastoma: A 12-Year Experience From a Single Center Study

Azim Mehrvar[1,2], Yasaman Sadeghi[1,3], Narjes Mehrvar[1,4], Mohammad Faranoush[1,5], Mardawij Alebouyeh[1], Mohsen Roozrokh[1,6], Maryam Tashvighi[1]

[1] *MAHAK Hematology Oncology Research Center (MAHAK-HORC), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2] *AJA Cancer Epidemiology Research and Treatment Center (AJA-CERTC), AJA University of Medical Sciences, Tehran, Iran*

[3] *Department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

[4] *Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[5] *Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran*

[6] *Pediatric Surgery Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Received: 11 May 2022; Accepted: 14 Mar. 2023

Abstract- In this cross-sectional study, we aimed to evaluate epidemiologic data, survival, and prognosis of pediatric patients diagnosed with neuroblastoma who were referred to Mahak Pediatric Cancer Treatment and Research Center (MPCTRC). One-hundred thirty-seven children younger than 15 years with neuroblastoma from April 2008 to March 2020 were included in this study. Data were retrospectively extracted from their documents, and follow-up was done for alive individuals. Collected data were analyzed using SPSS software version 25 for parametric and non-parametric variables. Of all patients, 51.82% (n=71) were male (M/F ratio was 1.07:1) with a mean age of 2.48±0.26 years. According to the International Neuroblastoma Staging System (INSS), more than 70% of patients were diagnosed with stages 3, 4, and 4S. Primary tumors were located mostly in the adrenal glands (42.34%) and abdomen (29.20%), respectively. Additionally, 62% of children experienced metastasis, with the most common site being bone marrow. Moreover, patients' overall survival, progression-free survival, and event-free survival were 55.2%±5.6, 41.0%±7.9, and 30.0%±5.1, respectively. Early diagnosis and effective treatment of neuroblastoma can directly influence patients' survival, and those who are diagnosed with neuroblastoma within one month of its symptoms onset are more likely to have higher survival rates.

Acta Med Iran 2023;61(5):275-281.

Keywords: Neuroblastoma; Pediatric oncology; Survival rates; Delayed diagnosis and treatment

Introduction

Neuroblastoma (NB) in children accounts for approximately 7.8% of childhood cancers in the United States and 0.4 million worldwide (1). It is claimed that around 650 to 700 new cases are annually diagnosed with NB in the United States, with an incidence of 8.6 pediatric patients per million children. This malignancy is estimated to have a 5-year relative survival rate of 80.6% for children of both female and male sexes younger than 19 years of old, 79.0% for males and 82.3% for females. Furthermore, amongst children diagnosed with NB, 55.1% are under 12 months of age, followed by 1-4 years old children, that constitute 21.8% of cases (1,2). There are limited numbers of studies in which childhood NB incidence and prevalence in Iran are reported. However, recent studies have demonstrated that NB accounts for 8.6% and 6.5% of childhood cancers in northwest and northeast Iran, respectively (3,4).

In order to have the best treatment process and to reduce NB mortality, early diagnosis of disease and quick referral to health care system is a crucial factor (5).

Corresponding Author: M. Tashvighi
MAHAK Hematology Oncology Research Center (MAHAK-HORC), Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 2123501344, E-mail address: m.tashvighi98@gmail.com

Furthermore, treatment failure or patient's poor prognosis could be the result of delayed referral to an oncologist, final and accurate diagnosis, and start of treatment.

This was a cross-sectional study in which we aimed to evaluate epidemiologic data and prognosis of patients diagnosed with neuroblastoma who were referred to Mahak Pediatric Cancer Treatment and Research Center (MPCTRC) for either diagnosis, treatment, following up or palliative care. MPCTRC is a non-governmental organization (NGO) that supports children with cancer and provides multidisciplinary treatment and care for pediatric patients in Iran and even other countries. By conducting this study, we also aimed to evaluate the management of patients with NB in terms of delay in diagnosis and treatment.

Materials and Methods

Patients

This retrospective study was conducted on 236 children who were diagnosed with neuroblastoma at MPCTR amongst a total number of 4201 hospitalized patients from April 2008 to March 2020. Patients younger than 15 years of old whose histologic type of disease was neuroblastoma were included in our study (137 patients), and older patients (n=2), and children diagnosed with other World Health Organization's histologic types such as Ganglioneuroblastoma and Ganglioneuroma (n=21), and children with Brain Neuroblastoma (CNS Embryonal Tumor, n=4) were excluded. Those referred to our center just for physician's visit were also excluded from the study (n=72).

Data collection

To collect data, we referred to patients' clinical documents, including different parts such as demographic information (name, gender and date of birth, familial history of cancer), early symptoms of disease and its onset date, date of starting first therapeutic procedure, any laboratory tests, any imaging process, treatment protocol, pathology reports, etc. All information was gathered by whether a pediatric hematologist-oncologist and a head nurse via interviewing patients and their families, as well as clinical tests.

Staging system

To better evaluation of patients, we used International Neuroblastoma Staging System (INSS), including stages 1, 2A, 2B, 3, 4 and 4S, and International Neuroblastoma Risk Group Staging System (INRGSS) including stages L1, L2, M, and MS

Referral, diagnosis and treatment delay

Diagnosis delay accounts for the time elapsed from symptoms onset to final diagnosis (earlier than 30 days was defined as early diagnosis and more than this time period was determined as late diagnosis). Treatment delay is explained as the time between final diagnosis and start of appropriate treatment (earlier than 14 days was defined as early treatment and more than this time period was determined as late treatment). Referral delay was defined as the time from the first surgery (biopsy or total resection of tumor) to referring him/her to an oncologist to start chemotherapy.

Survival and prognosis

Overall Survival (OS) was defined as the time between diagnosis and the last evaluation of patient. Progression Free Survival (PFS) was considered the time from diagnosis to relapse in order to illustrate patients without this event. Event Free Survival (EFS) was defined as the time from diagnosis to the first event, including relapse, metastasis or death.

Analysis

All the collected data was entered in SPSS software version 25. Descriptive analysis and T-test were used for both parametric and non-parametric data. Additionally, to perform the survival analysis, we used Kaplan-Meier test.

Results

Patients' demographic and clinical characteristics

Among 137 pediatric patients who had been referred to MPCTRC, 48.18% (n=66) were female and 51.82% (n=71) were male (M/F ratio was 1.07:1). Patients' age at the time of diagnosis ranged from 4 days to 14.7 years, and the mean age of enrolled patients was 2.48±0.26 years. The majority of patients (54.74%) were related to the age group of 2 to 4 years old followed by children younger than one-year-old (30.66%).

The most frequent symptom of NB among patients was pain (32.8%), followed by fever (20.4%), gastrointestinal disorders (19.7%), movement disorders (19.7%) and palpable abdominal mass (15.3%). Additionally, proptosis and periorbital ecchymosis made up less than 9% of all symptoms. Other symptoms, including weight loss, neonatal jaundice, weakness and paleness, urinary tract disorders and arthralgia were found sporadically among patients.

According to INSS, 10.22% of patients (n=14) had stage 1, 6.57% were in stage 2A (n=9), 8.03% were in stage 2B (n=11), 18.98% were in stage 3 (n=26), 40.15%

were in stage 4 (n=55) and 10.95% were in stage 4S (n=15). Moreover, NB staging was not determined for seven patients as their diagnosis was out of MPCTRC and their pathology report was not accessible. Furthermore, the majority of patients in advanced stages of NB were from one to four years old. Table 1 shows the demographic and clinical characteristics of patients due to their sex. Based on INRGSS, 13.87% of patients (n=19) were in the L1 risk group, 29.20% (n=40) were in the L2 risk group, 40.88% (n=56) were in the M risk group and 10.95% (n=15) were in the MS risk group.

Table 1. Patients' demographic information and clinical data at diagnosis

Variables		Female	Male	Total
Mean Age at Diagnosis (yrs.)		3.236±0.498	1.852±0.321	2.508±0.296
Age Group at Diagnosis	**<1 years**	11 (20.00%)	23 (37.70%)	35 (30.17%)
	1-4 years	32 (58.16%)	32 (52.46%)	72 (62.06%)
	5-9 years	6 (10.91%)	5 (8.20%)	16 (13.79%)
	10-15 years	6 (10.91%)	1 (1.64%)	7 (6.03%)
Primary Tumor Site	**Adrenal**	18 (32.73%)	25 (26.23%)	54 (46.55%)
	Abdominal	29 (52.73%)	16 (40.98%)	34 (29.31%)
	Thoracic	1 (1.82%)	4 (6.56%)	5 (4.31%)
	Cervical	2 (3.64%)	2 (3.28%)	4 (3.45%)
	Other Sites	5 (9.09%)	14 (22.95%)	19 (16.38%)
Neuroblastoma Stage (INSS)	**1**	3 (5.45%)	7 (11.48%)	10 (8.62%)
	2A	4 (7.27%)	2 (3.28%)	6 (5.17%)
	2B	5 (9.09%)	5 (8.20%)	10 (8.62%)
	3	13 (23.64%)	10 (16.39%)	23 (19.83%)
	4	22 (40.00%)	27 (44.26%)	49 (42.24%)
	4S	6 (10.91%)	7 (11.48%)	13 (11.21%)
	Not Determined	2 (3.64%)	3 (4.29%)	5 (4.31%)

Regarding molecular characteristics, we evaluated *N-myc* gene amplification and ploidy as well as deletion of the long arm of chromosome 11 (11q deletion). Unfortunately, *N-myc* gene amplification was conducted only on 77 patients since the method of this evaluation has been set up in our hospital for 6 years and the majority of patients were diagnosed with neuroblastoma before this time. Regarding those whose *N-myc* gene were evaluated, 51 patients had the normal status (<2-fold increase (Wild-type) and 2-4-fold increase (MYCN gain (Inconclusive))), and 26 patients had *N-myc* gene amplification. A number of 14 and 12 patients with *N-myc* gene amplification were categorized as 5-10-fold increase (low-level MNA) and >10-fold increase (high-level MNA), respectively.

Primary tumor sites and stages of the disease

Although primary tumor sites of patients varied in different cases, it was significantly located in the adrenal glands (42.34%) and abdomen (29.20%). Tumors of the thoracic and cervical regions made up 10.95% and 2.92% respectively. In 14.60% of cases, tumors were located in other sites of body, including liver, orbits, femur, etc. Patients' symptoms based on their primary site of neuroblastoma are also shown in Table 2.

Metastasis

Out of enrolled patients, 62% (n=86) experienced metastasis. The commonest sites of metastasis were bone marrow (33.7%) and bones (20.9%) respectively. The mean time between diagnosis and the first metastasis was 4.67±1.1 months, with a maximum of 71 months. The relation between metastatic sites and primary tumor sites in considered patients is shown in Table 2. The Overall survival of patients who never experienced metastasis had an OS of 73.4±6.7% while the OS of those who had one metastasis was 54.8±9.0%. Furthermore, of 86 patients with metastasis, 32.5% (n=28) had metastasis in more than one site of their body and their OS dramatically decreased to 20.7±11.3%. Most of these patients (53.57%) were female, with a mean age of 4.50±0.80 years. Based on INSS staging, stage 4 was the commonest stage (71.43%) of NB in patients who experienced more than one metastasis. They also had a 5-year Overall Survival of 20.7%±11.3.

Follow-up and survivals

Out of enrolled patients, 48 children, including 21 males and 27 females, died. The mean time of follow up was 34.8±2.90 months with the maximum of 168 months. The 5-year overall survival rate of patients was 55.2%±5.6. Additionally, one-year PFS was 41.0%±7.9, and 1-year EFS was 30.0%±5.1. Survival data for each sex is shown in details in Table 3. Data about OS based

on patients' demographic and clinical characteristics are shown in Table 4.

Table 2. Patients' primary symptoms and site of first metastasis based on their primary tumor site

		Primary Tumor Site					
		Abdominal	Adrenal	Thoracic	Cervical	Others	Total
Symptoms	Pain	16	15	1	-	9	41
	Fever	7	12	1	-	5	25
	Gastrointestinal Disorders	6	11	-	1	3	21
	Palpable Abdominal Mass	6	8	1	1	2	18
	Movement Disorders	7	7	3	-	2	19
	Proptosis	-	2	-	1	5	8
	Periorbital Ecchymosis	-	-	-	-	2	2
	Other Symptoms	14	20	4	3	8	49
Site of First Metastasis	Bone Marrow	3	9	2	-	10	24
	Cortical Bone	4	8	1	1	2	16
	Central Nervous System	3	3	-	-	1	7
	Liver	6	3	-	-	2	9
	Lymph nodes	1	5	-	1	-	7
	Lungs	1	1	-	-	2	4
	Skin and Subcutaneous	-	-	-	1	1	2
	Others	1	3	-	-	-	4

Table 3. Patients' follow-up information, OS, EFS and PFS based on gender

Variables		Female	Male	Total
Patients Status in latest follow-up	Off-treatment	17 (30.91%)	23 (37.70%)	40 (34.48%)
	Dead	26 (47.27%)	20 (32.79%)	46 (39.66%)
	During treatment	2 (3.64%)	7 (11.48%)	9 (7.76%)
	Referred to their living city	10 (18.18%)	11 (18.03%)	21 (18.10%)
Mean Time of Follow-up (month)		29.87±3.81	36.88±4.53	34.8±2.90
Overall survival	1-year	80.7±5.5%	87.4±4.5%	94.8±2.1%
	3-year	54.6±7.6%	70.2±6.6%	83.4±3.5%
	5-year	40.7±8.3%	49.8±9.9%	69.5±4.6%
Event Free Survival	1-year	53.3±9.1%	55.6±9.6%	78.9±5.4%
Progression Free Survival	1-year	62.5±17.1%	53.8±13.5%	57.1±10.8%

Table 4. Overall Survival of male, female and total patients based on their demographic and clinical characteristics

Variables		Overall Survival		
		Female Patients	Male Patients	Total Patients
Age Group at Diagnosis	<1 years	90.9±8.7%	85.4±7.8%	87.1±6.0%
	1-4 years	32.4±10.3%	40.9±12.1%	35.8±8.2%
	5-9 years	26.7±22.6%	66.7±27.2%	45.0±19.0%
	10-15 years	22.2±19.2%	85.7±13.2%	37.7±19.8%
Primary Tumor Site	Adrenal	33.3±13.4%	34.8±17.2%	33.8±11.1%
	Abdominal	47.1±12.3%	93.8±6.1%	64.3±9.6%
	Thoracic	-	-	-
	Cervical	-	-	-
	Other Sites	40.0±21.9%	44.2±14.4%	41.9±12.2%
Neuroblastoma Stage (INSS)	1	-	85.7±13.2%	85.7±13.2%
	2A	50.0±35.4%	-	50.0±35.4%
	2B	-	78.8±13.4%	78.8±13.4%
	3	36.1±15.4%	62.2±17.8%	47.5±12.2%
	4	26.4±11.7%	42.0±14.8%	34.1±9.3%
	4S	66.7±19.2%	85.7±13.2%	76.2±12.1%

Referral, diagnosis and treatment delay

Regarding diagnosis delay, the time between symptoms onset and diagnosis of disease ranged from 2 days to 37.2 months with a mean of 69.8±12.0 days. In addition, considering treatment delay, the meantime elapsed from the final diagnosis of the disease to the first treatment date (either total resection of tumor via surgery or chemotherapy) was 18.2±5.2 days with a maximum of 13.6 months, although four patients started chemotherapy regimen before their final diagnosis. There was no

significant correlation between delay in diagnosis or treatment with any demographic data, such as age and sex, or clinical data, such as the stage of the disease. Information about the survival of patients based on their diagnosis or treatment delay is shown in Table 5.

Regarding referral delay, of total 137 patients, 109 patients underwent surgery (biopsy or total resection of tumor) before chemotherapy with a referral delay of a maximum of 15.3 months. Their one-year, 3-year and 5-year OS was 83.8%±3.7, 65.2%±5.2 and 54.6%±6.2, respectively. Additionally, one-year PFS and one-year EFS were 40.7%±9.5 and 12.2%±3.6, respectively. Other patients either never experienced any kind of surgery (n=9), never received chemotherapy (n=6), or had a neoadjuvant therapy and received chemotherapy before their surgery (n=13).

Table 5. Delay in diagnosis and treatment

Variables		Diagnosis		Treatment	
		Early	Late	Early	Late
Overall Survival	1-year	87.3±4.5%	81.0±5.4%	85.1±4.0%	77.9±8.8%
	3-year	64.9±6.7%	59.0±7.9%	64.1±6.0%	58.4±10.7%
	5-year	51.9±8.0%	49.3±9.2%	48.2±7.3%	58.4±10.7%
Event Free Survival	1-year	61.3±8.7%	53.8±9.8%	57.1±7.6%	50.0±14.4%
Progression Free Survival	1-year	57.1±13.2%	57.1±18.7%	60.0±12.6%	66.7±27.2%

Discussion

Our study was designed at Mahak Pediatric Cancer Treatment and Research Center (MPCTR) on 137 pediatric patients diagnosed with neuroblastoma. Mahak Hospital is an NGO multidisciplinary center established for children with different types of malignancies, whether Iranian or from other nationalities. The whole therapeutic process for these children from diagnosis to treatment and regular follow-ups is conducted free of charge in this center. Furthermore, Mahak Hospital is the only referral center in Iran for pediatric patients who develop any kind of malignancy.

Male patients formed most of our study population, accounting for 51.82% of cases, which is approximately similar to other studies (6,7). According to the American Cancer Society, 90% of cases are diagnosed with NB by the age of 5 years, which can act as a support for our results that the majority of patients were from 1 to 4 years of age (8). The commonest site of neuroblastoma was the adrenal glands followed by the abdomen. This outcome was similar in most studies (9-12), although in some studies the abdomen was the primary site of this disease (7).

The overall survival of children diagnosed with neuroblastoma varies based on their risk groups; however, it can range from 40% to 95% (2). In our study, the 5-year overall survival was 55.2±5.6%, and male patients had higher OS than female ones. This outcome was the same as another study published by Oxford University Press that focused on differences of survival between male and female pediatric patients, in which the OS for males was 51.7% while females had the OS of 48.3% (6). Additionally, some studies have analyzed the survival of NB patients in Iran. For instance, a study on 219 children at Ali Asghar's Hospital demonstrated that female patients had better cumulative survival (56±8%) than males (36±8%) (12).

Metastasis in neuroblastoma plays a key role in patients' survival rates as in our study those who never experienced metastasis had an OS of 73.4±6.7%, while the OS of those who had one metastasis was 54.8±9.0%. This means that metastasis significantly influenced the OS of patients, and for those who had more than one metastasis during their disease, the OS dramatically decreased to 20.7±11.3%.

N-*myc* gene amplification could be another critical factor in the overall survival of patients with neuroblastoma. Precisely, the progression of patients who had N-*myc* gene amplification considers to be worse than those with normal N-*myc* gene status (13). Unfortunately, we had missed information on this factor based on the fact that evaluating the amplification of this gene was not set up in our hospital for a long time, which resulted in missing the data for almost half of the patients (n=60). Therefore, we are unable to have a meaningful comparison of the relationship between the N-*myc* gene amplification and patients' survival rates with other studies.

In our study, infants younger than one-year-old had the greatest overall survival rate (89.1±5.2%) and patients aged one to 4 years old had the lowest OS (30.3±9.1%). It could be as a result of this fact that NB is more common in 1 to 4 years old children and the majority of them are

diagnosed with advanced stages. In relation to the INSS staging system, the overall survival of patients was higher in the initial stages of NB (stage 1, 2A and 2B) and stage 4S, while in advanced stages the OS decreased significantly. Since stage 4S is related to infants (under one-year-old) and the survival of these patients is already higher than other age groups, lower OS in advanced stages (stages 3 and 4) could illustrate the aggressiveness of NB.

One of the most crucial factors in reducing the mortality of childhood cancer is early diagnosis and treatment (5). In this study, we evaluated delays in both the diagnosis of the disease and the onset of treatment process. According to Table 5, the 5-year overall survival of patients who were diagnosed with NB maximally a month after their symptom onset (early diagnosis group) was higher than those with later diagnosis (late diagnosis group). This outcome seems to be true for EFS, which means that those who are diagnosed with NB earlier may experience relapse, metastasis or even death later than the other group. The comparison of PFS between the early and late diagnosis group; however, did not show a difference in our study and the results of both group were approximately the same. In a study conducted in Southern Brazil, it was claimed that the OS of patients over an 11-year period was influenced by their diagnosis time, and those with delayed diagnosis had lower survival rates than others (14).

According to results of survivals based on delay in treatment, 1-year and 3-year OS was higher in patients with early treatment process (therapeutic measures within 14 days after diagnosis), while the 5-year OS was lower. As same as delay in diagnosis, the EFS is higher in the early group, which means that they may undergo those events at a further time. Nonetheless, the PFS for patients with delay in treatment more than two weeks was unexpectedly higher than the other group.

Overall, it seems that early diagnosis and effective treatment of neuroblastoma can directly influence patients' survival, and those who are diagnosed with this disease within a month of its symptoms onset are more likely to have higher survival rates in comparison with pediatrics whose malignancies are diagnosed later. Timely diagnosis and treatment of NB also reduce the risk of metastasis which in turn leads to higher overall survival. Consequently, increasing awareness of this disease among parents could be a new frontier to the diagnosis of neuroblastoma as soon as possible. Since this disease is more common in children younger than 4 years old, accurate monitoring of children in this age group could be beneficial in better diagnosis of neuroblastoma. Finally, we strongly recommend further multi-central studies including other aspects of delay in diagnosis such as patient or parental delay as well as evaluating treatment protocols of the disease in order to have better understanding of the factors that can affect patients' survival and progression.

Acknowledgements

This research was supported by Mahak Hematology Oncology Research Center (Mahak-HORC).

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