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Long-Term Outcomes Of Patients With Stage IV Neuroblastoma(NB) In Bangladesh Shishu Hospital

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Abstract

Background: Long-term outcome studies in survivors with stage IV neuroblastoma (NB) are poor. This study evaluates long-term outcomes and late complications in stage IV NB survivors in Bangladesh Shishu Hospital.

Methods: This prospective observational study was done in Bangladesh Shishu Hospital and Institute(BSH & I) from January 2020 to December 2024. We have 55 stage IV NB patients, treatment was started with metronomic therapy, analysis done for outcomes. All 55 patients were treated with metronomic treatment for 364 days. Each cycle 28 days, drugs used are propranolol, vinblstine, cyclophosphamide, etoposide and one NSAID(instead of celecoxib) drug if pain.

Results: Among the study population,10 were survived and survival rate was 18.18%, 5 were male and 5 female patients. Among the 10 survival patients 6 were diagnosed within 18 months of age and remaining 4 were more than 18 months of age. Regarding Primary tumor sites 38 patients with adrenal gland (69%), 11 with retroperitoneal (20%), pelvic mass in 4(7.3%) and 2(3.64%)with mediastinal mass. Total 25 patients (45.45%) developed metastases among them bone marrow 10(18.18%), liver7(12.73%), Bone 5(9%) and skin 3(5.45%). Twenty patients had tumor recurrence among them 6 patients survived. Recurrence was retroperitoneal 9, Orbit 6 and Adrenal gland 5 cases and was treated by resection, chemotherapy, and radiation. The mean age of survivors was 6±1.9 years (range, 2-8 years). In all stage IV cases, event-free survival was 15% and overall survival was 18%. Sixty percent (6) of survivors experienced late morbidity, and tumor recurrence in 4 cases(40%) of survival. Long-term complications occurred in 6(60%) survivors, including endocrine disturbances (3), orthopedic (1), cataracts (1) and adhesive bowel obstruction (1).

Conclusion: Only 10(18.18%) patients with stage IV NB survived with metronomic therapy. Age of younger than 18 months, favorable histology, operative treatment and no recurrence were the only statistically significant factors that favored survival. Sixty percent (6) of survivors experienced late morbidity, and tumor recurred in 20 (36.36%) of 55 patients, among them 4 in survivor group. Patients should be monitored for tumor recurrence and long-term sequelae. New methods of treatment are required to achieve better outcomes.

Keywords: Neuroblastoma; Complete tumor resection; Stem cell transplantation; Outcomes

1. Introduction

Most children with neuroblastoma (NB) present with advanced, often unresectable metastatic disease **[1]**. Historically, survival for patients with stage IV is poor. Prognostic factors used to determine severity/treatment of NB are composed of clinical, biologic, and molecular parameters **[2]**. The natural history of NB follows 1 of 3 pathways: tumor progression, tumor maturation to a benign ganglioneuroma, or spontaneous regression **[2]**. Unfortunately, a significant number of patients have a progressive clinical course. A variety of reports showed improved survival in patients with stage IV NB receiving intensive chemotherapy and stem cell/bone marrow transplantation **[3-6]**. However, information concerning long-term outcomes in survivors of stage IV NB is relatively poor **[1]**.

Patients and Methods:

This prospective observational study done on 55 patients with stage IV NB from January 2020 to December 2024 at Hematology and Oncology department of Bangladesh Shishu Hospital and Institute, Dhaka. After receiving informed written consent, detailed history, physical examination, relevant investigation reports and treatment protocol were recorded in a questionnaire. For each patient 24 hours urinary VMA, USG/CT scan of abdomen, CXR or chest CT, liver and renal function test, bilateral bone marrow, CNS imaging if symptoms, tissue biopsy for histopathology and immunohistochemistry. Bone scan was done before treatment or after treatment or during bony symptoms were present, result were recorded in questionnaire. All study population(n-55) were treated with metronomic therapy after confirmation of diagnosis, some patients required surgery/radiotherapy along with chemotherapy. Survivors were

defined as all patients alive at time of follow up. Data for the 2 groups (survivors and nonsurvivors) were compared using the Fisher's Exact test. Values are expressed as mean. Significance is set at the 95% confidence interval (p value .05). Ethical review committee of BSH & I was approved the study design.

2. Results

Fifty five patients were diagnosed with stage IV NB. Ten (18.18%) survived, among them 5 were male and 5 female. Demographics are summarized in **(Table 1)**. Age at diagnosis <18 months survival is higher than those diagnosed after 18 months. For patients presenting 18 months or younger, survival was 6 (60%) of 10 compared with a survival of 4 (8.9%) of 45 (P =0 .001) in patients presenting older than 18 months. Prognosis also better in female gender than male, from 25 female patients 5 were survived, rate was 20%, from 30 male patients 5 were survived, rate was 16.67%, survival rate compared in both group is significant, p value 0.002. Primary tumor sites for survivors and nonsurvivors are shown in **(Table 2)**. Sites of metastasis in survivors and nonsurvivors are shown in **(Table 4)**. Sites of metastasis in survivors and nonsurvivors were similar. All primary NBs were assigned a histological classification **[11]** at Bangladesh Shishu Hospital. Of 10 patients, 7 (70%) with favorable histology and of 45, 3 (6.67%) with unfavorable histology survived (P = 0.001). Treatment in survivors included surgery in 3(30%),chemotherapy, 5(50%), radiation 2(20%). Tumor resection required nephrectomy in 2 patients. Six survivors had operative treatment followed by adjuvant chemotherapy. There were 2 instances of postoperative retroperitoneal bleeding. Chemotherapeutic administration in each instance followed approved Children's Cancer Group protocols(Metronomic therapy) in use at the time. Fourty patients had tumor recurrence and 3 survived. The mean age at recurrence was 3± 1 years (range, 6 months–15 years).

Table 1: Demographics of survivors and nonsurvivors with stage IV NB

Demographics		Survivors(%)	Nonsurvivors(%)	P value
Age	<18 months	6/30(20)	24/30(80)	0.001
	>18 months	4/25(16)	21/25(84)	
Gender	Male	05(14.29)	30(54.50)	0.002
	Female	05(25)	25(45.50)	
Residence	Rural	06(17.14)	35(63.64)	0.55
	Urban	04(20)	20(36.36)	
Economic status	Poor	03(12)	22(88)	0.34
	Middle class	04(20)	16(80)	
	Higher class	03(30)	07(70)	

Table 2: Primary tumor sites for survivors and nonsurvivors

Primary tumor sites	Survivors (%)	Non survivors (%)	Total (%)
Adrenal	8(80)	30(66.67)	38(69)
Retroperitoneal	1(10)	10(22.22)	11(20)
Mediastinal	0	2(4.44)	2(3.64)
Pelvic	1(10)	3(6.67)	4(7.3)

Majority tumor having primary site in adrenal gland

Table 3: Clinical and laboratory parameter affecting outcome

Data point	Survivors	Nonsurvivors	P value
Age<18 months at diagnosis	20% (6/30)	80% (24/30)	0.001
Operation done prior to chemotherapy	50 (5/10)	22.22(10/45)	0.23
High urinary VMA	40 (4/10)	55.56 (25/45)	0.43
Favorable histology	70 (07/10)	26.67 (12/45)	0.001
Tumor recurrence	30 (3/10)	82.22 (37/45)	0.001

Values are presented as percentage (n).

Table 4: Sites of metastasis for survivors and nonsurvivors

Sites of metastasis	Survivors(%)	Non survivors(%)	Total(%)
Skin	1(10)	2(4.44)	3(5.45)
Liver	1(10)	6(13.33)	7(12.73)
Bone marrow	2(20)	8(17.78)	10(18.18)
Bone	0	5(11.11)	5(9)

Table 5: Outcome of study population(n-55)

Outcome		Number of patients	Percentage(%)
Overall survival(3 years)		10/55	18.18
Event free survival(3 years)		8/55	14.54%
Recurrence of tumor (20)	Retroperitoneal	9/20	45%
	Orbit	6/20	30%
	Adrenal gland	5/20	25%
Long term complications (6)	Endocrine disturbances	3/6	50%
	Orthopedic	1/6	16.67%
	Cataract	1/6	16.67%
	Bowel obstruction	1/6	16.67%
Death (45)		45/55	81.82%

Retroperitoneal recurrent site is treated by adrenalectomy with resection of retroperitoneal tumor. Orbital and new adrenal mass treated by adrenalectomy and tumor resection, chemotherapy, and radiation. In all 55 stage IV cases, event-free survival was 14.54% and overall survival was 18.18%. The length of survival in survivors was 2 to 5 years. Long- term complications occurred in 6 (60%) of survivors, including endocrine disturbances (3), orthopedic (1), post radiation cataracts (1), adhesive bowel obstruction (1). The mean age at death of nonsurvivors was 3±1.8 years (range, 3 months–6 years). The principle causes of death were either a result of metastatic disease (heart failure, respiratory failure, brainstem herniation, and others) or sepsis.

3. Discussion

Most studies reviewing long-term outcomes in stage IV NB concentrate on the effect MYCN amplification and chemotherapeutic regimens have on survival **[3-7]**. Currently, the search for biomarkers to diagnose tumor presence and determine prognosis in advanced NB dominates the literature **[8-10]**. However, reports on long-term outcomes in stage IV NB are relatively infrequent. The age at diagnosis of NB is one of the single most important indicators of survival **[2,11,12]**. Age (at diagnosis) of younger than 18 months is associated with increased survival. This series supports other published studies with a statistically significant number of children diagnosed before 18 months of age surviving even in the presence of metastatic disease. Primary tumor sites and sites of metastasis were similar in survivors and nonsurvivors and did not appear to confer a survival advantage. In our study, 3 patients had skin metastases, 1 in the survivor group and 2 in the non-survivor group. A small number of patients were stratified according to the histological classification **[7]**. Tumors are either stroma- poor or stroma-rich according to their organizational pattern (stromal development). The stroma-poor group is further classified into favorable and unfavorable according to age of diagnosis, degree of maturation, and nuclear pathology (mitosis-karyorrhexis index) of the neuroblastic cells. The stroma-rich group is further classified into well differentiated, intermixed, or nodular on the basis of morphology of the immature element in the tumor tissue regardless of patient age or quantitative maturation. Favorable stroma-poor and well-differentiated and intermixed stroma-rich groups comprise the good prognosis groups. Unfavorable stroma-poor and nodular stroma-rich groups are considered poor prognosis groups and show morphological evidence of malignant or aggressive behavior, such as inappropriate immaturity for age, higher mitosis-karyorrhexis index, and gross nodule formation by immature neuroblasts. A statistically significant increase in favorable histology was observed in survivors compared with nonsurvivors. However, there were still several survivors that had unfavorable histology. Stem cell/bone marrow transplantation did not confer a statistically significant survival benefit. Although operative treatment in metastatic disease is a controversial issue, operative treatment did impart a significant survival advantage in patients with stage IV NB, regardless of age at diagnosis. La Quaglia et al **[13]** reported improved local control and overall survival rates with complete gross resection of the primary tumor in stage IV NB. Microscopic margins may be positive for tumor **[13]** because dissection is accomplished in the pseudocapsular plane. Although the role of aggressive tumor

resection has been controversial **[14,15,16]**, our series supports the findings of improved survival with operative treatment in patients with high-risk NB. Although large en bloc resections encompassing surrounding major structures are avoided when possible, 3 (25%) of 12 patients with operative treatment required nephrectomy. Complete tumor resection is recommended whenever possible in stage IV NB. There were 3 stage IV survivors after tumor recurrence in this series. One had complete resections, one was treated with chemotherapy, and one with radiation. Follow-up postrecurrence ranged from 1 month to 6 years (age at survival, 3-10 years). Of the 3 patients, 2 were noted to be disease-free at last noted follow-up. Recurrence occurred between 1 and 2 years of age in most patients (survivors and nonsurvivors). There appeared to be no survival benefit related to time of recurrence. However, only 2 (5%) of the 30 recurrences occurred more than 2 years after the original diagnosis. It appears that if a patient survives past 5 years, it is much less likely that their tumor will recur. Event-free survival was 14.54% and overall survival was 18.18% in the 55 patients with stage IV NB. A significant number of surviving patients (60%) had sequelae of the treatment modalities, including surgery (adrenal insufficiency), chemotherapy (other endocrine disturbances, peripheral neuropathy), and radiation (blindness, cataracts. Age of younger than 18 months, operative treatment, favorable histology and no recurrence favor survival. Sixty percent of survivors experienced late morbidity, and tumor recurrence in 54.54%.

Conclusion

Only 18.18% patients survived with metronomic therapy for stage IV neuroblastoma but majority get relapsed. Long-term follow-up is necessary to monitor for tumor recurrence and long-term sequelae. Other new and novel treatments (i.e., differentiating agents, antiangiogenic and proapoptotic therapies, and immunologic modulators) are required to improve the outcomes of children with stage IV disease and reduce the untoward effect of current therapies.

References

1. Pinto NR, Applebaum MA, Volchenboum SL, Matthay KK, London WB, et al. (2015) Advances in risk classification and treatment strategies for neuroblastoma. J Clin Oncol. 33(27): 3008-17.
2. Grosfeld JL (2000) Risk-based management of solid tumors in children. Am J Surg. 180(5): 322-7.
3. Kaneko M, Tsuchida Y, Mugishima H, Ohnuma N, Yamamoto K, et al. (2002) Intensified chemotherapy increases the survival rates in patients with stage 4 neuroblastoma with MYCN amplification. J Pediatr Hematol Oncol. 24(8): 613-21.
4. Kawa K, Ohnuma N, Kaneko M, Yamamoto K, Etoh T, et al. (1999) Long-term survivors of advanced neuroblastoma with MYCN amplification: a report of 19 patients surviving disease-free for more than 66 months. J Clin Oncol. 17(10): 3216-20.
5. Tweddle DA, Pinkerton CR, Lewis IJ, Ellershaw C, Cole M, et al. (2001) OPEC/OJEC for stage 4 neuroblastoma in children over 1 year of age. Med Pediatr Oncol. 36(1): 239-42.
6. Kaneko M, Nishihira H, Mugishima H, Ohnuma N, Nakada K, et al. (1998) Stratification of treatment of stage 4 neuroblastoma patients based on N-myc amplification status. Med Pediatr Oncol. 31(1): 1-7.
7. Shimada H, Chatten J, Newton WA Jr, Sachs N, Hamoudi AB, et al. (1984) Histopathologic prognostic factors in neuroblastic tumors: definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblas- tomas. J Natl Cancer Inst. 73(2): 405-16.
8. Selig RA, Madafiglio J, Haber M, Norris MD, White L, et al. (1993) Ferritin production and desferrioxamine cytotoxicity in human neuroblastoma cell lines. Anticancer Res. 13(3): 721-5.
9. Quinn JJ, Altman AJ, Frantz CN (1980) Serum lactic dehydrogenase, an indicator of tumor activity in neuroblastoma. J Pediatr. 97(1): 89-91.
10. Nakagawara A (2001) Trk receptor tyrosine kinases: a bridge between cancer and neural development. Cancer Lett. 169(2): 107-14.
11. Grosfeld JL (1986) Neuroblastoma in infants and childhood. Hays DM, editor. Pediatric surgical oncology. Orlando, FL7 Grune & Stratton; 63.
12. Grosfeld JL, Rescorla FJ, West KW, Goldman J (1993) Neuroblastoma in the first year of life: clinical and biologic factors influencing outcome. Semin Pediatr Surg. 2(1): 37-46.
13. La Quaglia MP, Kushner BH, Su W, Heller G, Kramer K, et al. (2004) The impact of gross total resection on local control and survival in high-risk neuroblastoma. J Pediatr Surg. 39(3): 412-7.
14. Kiely EM (1993) Radical surgery for abdominal neuroblastoma. Semin Surg Oncol. 9(6): 489 - 92.
15. Kaneko M, Ohakawa H, Iwakawa M (1997) Is extensive surgery required for treatment of advanced neuroblastoma? J Pediatr Surg. 32(11): 1616-9.
16. Holmes K, Pötschger U, Pearson ADJ, Sarnacki S, Cecchetto G, et al. (2020) Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study. J Clin Oncol. 38(25): 2902-2915.