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Original Article

Clinical Spectrum of Advanced Neuroblastoma

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Abstract

Background: **To analyze the spectrum of neuroblastoma and burden of high risk malignancy on the public sector tertiary center.**

Methods: **In this descriptive study, 70 patients with neuroblastoma were enrolled. Data regarding their age, sex, type (infantile <547 days or 18 months or more than 18 months), staging and clinical features, bone and bone marrow involvement, course of therapy and outcome was analyzed . The staging was done on the basis of bilateral bone marrow biopsy and imaging CT Scans, MRI neck chest and abdomen and bone scans. Patients were treated with conventional vincristine, cyclophosphamide, doxorubicin, etoposide and carboplatin for 6-8 courses 2-3 weeks apart depending upon the age whether 18 months or older group. Evaluation was done after 2-4 courses to see the response and options for surgery by doing imaging in the form of MRI or CT scans.**

Results: **Total 70 patients with age ranging from< 1 year to 15 years (median age of 3 yrs) were included. M: F Ratio was 1.8:1. Non-infantile type (70%), stage IV (79%) and adrenal mass (47%) were the commonest presentations. Bone and bone marrow involvement was seen in 53% and 70% , respectively. Thirty out of seventy (43%) successfully completed the chemotherapy, 12/70(17%) abandoned treatment, 17/70 (24%) expired due to progressive disease and infections, 7/70(10%) were put on palliative treatment at presentation 4/70(6%) relapsed and given palliation therapy.**

Conclusion: **In resource limited settings, neuroblastoma stage IV is a challenging malignancy to deal with. There is intense need of increased capacity building to diagnose them early and implementation of effective infection control measures with better survival options in these patients.**

Key Words: **Neuroblastoma, Low income Countries**

Introduction

Neuroblastoma is the most common extracranial solid tumor in childhood in high income countries , where it accounts for 10% of pediatric cancers. [1] In low- and middle- income countries (LMIC) with population-based registries, it accounts for only 1–3% of cancers, and in most LMIC its true incidence is unknown. [2-4] Neuroblastoma is the most common extracranial solid tumour in childhood, accounting for 50% of neoplasms diagnosed in the first year of life. [5] Neuroblastoma is the most common neonatal solid tumour (47%) followed by germ cell tumours 28.8% in France in a study done from 2000-2009 with overall survival of 84% and most common site is abdomen 86% followed by chest and neck. [6] Neuroblastoma, the second most common childhood solid tumour, accounts for 8% of all childhood (0–14 years) cancers in the United Kingdom. However, survival remains poor for children diagnosed with high-risk disease (50% of all neuroblastoma).[7]

This disease has a heterogeneous course, ranging from spontaneous regression to inexorable progression and death, depending on the biologic features of the tumor. Identification of risk groups on the basis of clinical and molecular prognostic variables has allowed tailoring of therapy to improve outcomes and minimize the risk of deleterious consequences of therapy.[8] Neuroblastoma is notable for its broad range of clinical behaviors. Tailored treatment approaches, based on the presence or absence of specific clinical and biologic factors, have been used for decades, and successive institutional and cooperative group risk based clinical trials have led to substantial improvement in outcome for patients classified as low or intermediate risk**.** [9] Outcomes for the vast majority of patients with low-stage (International Neuroblastoma Staging System [INSS] stages 1 and 2) neuroblastoma are excellent. Local recurrences can typically be managed with surgery and/or radiation therapy. Metastatic recurrences are rare and often treated successfully with chemotherapy. Treatment of

patients with localized neuroblastoma with unfavourable biologic features is controversial. Among patients with low-stage, MYCN-amplified neuroblastoma, outcomes of patients with hyperdiploid tumors were statistically, significantly better than those with diploid tumors.[10] Advanced neuroblastoma is a systemic disease that spreads to the whole body, including the bone marrow, liver, lymph nodes, and bones. Morphologic or radiologic methods only detect metastases larger than a certain size. This indicates that high-risk neuroblastoma should be considered as a systemic disease and that an increase of chemotherapy intensity is a premise for the improvement of treatment outcome. High dose chemotherapy (HDC), with stem cell salvage following intensive induction chemotherapy has been widely accepted as being required for neuroblastoma treatment in high-risk groups, and treatment results have improved. However, the 5-year event-free survival (EFS) rate is 30–40% and remains unsatisfactory despite various intensive efforts. [9, 11]In low income countries like Pakistan advanced neuroblastoma, with dismal outcome, at presentation is more common.

Patients and Methods

In this descriptive study, performed in the department of Paediatric Haematology/ Oncology of the Children's Hospital Lahore from June 2015 to December 2016, patients with neuroblastoma were enrolled. Data regarding their age, sex, type (infantile <547 days or 18 months or more than 18 months), staging and clinical features, bone and bone marrow involvement, course of therapy and outcome was analyzed. Criteria of entry were children with diagnosis of neuroblastoma based on physical examination, basic laboratory, radiographic and pathologic evaluation along with immunohistochemistry (IHC) in all cases. The staging was done on the basis of bilateral bone marrow biopsy and imaging CT Scans, MRI neck chest and abdomen and bone scans. Patients were treated with conventional vincristine, cyclophosphamide, doxorubicin, etoposide and carboplatin for 6-8 courses 2-3 weeks apart depending upon the age whether 18 months or older group. Evaluation was done after 2-4 courses to see the response and options for surgery by doing imaging in the form of MRI or CT scans. No facility was available in our center for myeloablative chemotherapy with autologous hematopoietic stem cell rescue and immunotherapy for minimal residual disease to decrease relapse in high risk disease.

Results

Total 70 patients with age ranging from< 1 year to 15 years (median age of 3 yrs) were included. Five patients were more than 10 years (7%). M: F Ratio was 1.8:1. Forty nine cases were of non-infantile type(>18 months old) and 21 (30%) with infantile type (>18months).Fifteen (22%) had stage III at presentation while 55 (78%) was of stage IV. No one presented at stage I or II. Thirty three (47%) had mainly adrenal mass as the main presenting complaint, 5 (7%) as paraplegia, 4 (6%) as nasal polyp, neck and mediastinal involvement , 2 (3%) as bony masses and proptosis, 26 (37%)with multiple presentations. Fifty two (74%) had to travel more than 100 km to reach the primary treatment center. Thirty seven (53%) had bone involvement at presentation and 49(70%) had bone marrow involvement. Thirty (43%) had successfully completed the chemotherapy followed by surgical resection and radiotherapy if required for residual tumour, 12 (17%) abandoned treatment, 17 (24%) expired due to progressive disease and infections, 7(10%) were put on palliative therapy at presentation 4 (6%) were put on palliation after relapse (Table 1 &2).

Table 1: Staging and Outcome

Stage	treatment Complete	treatment Abandoned	Expired	Palliation on arrival	Palliation after Relapse	
III	7	0	6	0	2	15
IV	23	12	11	7	2	55
Total	30	12	17	7	4	70

p-value-0.05

Table 2: Staging and clinical spectrum

Stage	Adrenal mass	Multiple presentations	Non-Adrenal masses	Total	
Stage III	9	1	5	15	p-value=0.019
Stage IV	24	25	6	55	
total	33	26	11	70	
%	47%	37%	16%		

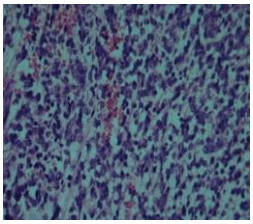

Figure 1: Round Blue Cell Tumour

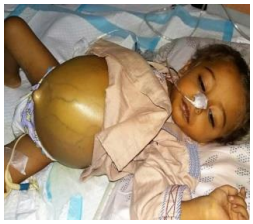

Figure 2: Advanced stage Neuroblastoma at presentation

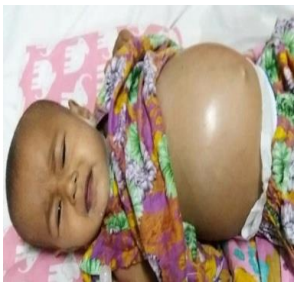

Figure 3: Infantile neuroblastoma

Figure 4: Bony Metastases and right proptosis at presentation.

Discussion

This is the most common extra-cranial solid tumour in West, however it is 4th most common solid tumour after lymphomas and Wilms tumor in our center. Neuroblastoma is uncommon in Africa with Burkitt's lymphoma being the commonest, but when seen usually presents as high-risk disease with a poor prognosis with overall survival of 4%. This aggressive biology of the tumor is frequently augmented by delayed presentation. Current treatment depends upon technologies and skills that are scarce in developing countries and the cost involved is generally beyond the means of healthcare providers who are faced with a myriad more pressing healthcare issues. [12] It is more common in males almost twice than females in our study as compared to SEER pediatric monograph illustrated that the overall incidence among males was 6.5% higher compared with that of females.[13] Seventy percent presented at older age group > 18 months in our study as compared to data analyzed in over 8800 children with neuroblastoma from 1999-2002 and 17% having stage III, 43% presented at >18 months age with age < 18 months having prognostic value with better 5-year overall survival of 95% than 76% in older age group having INSS stage III cohort (p-value=<0.001).[14] NB incidence peaks in infancy and then rapidly declines, with less than 5% of cases diagnosed in children and adolescents >10 years. There is increasing evidence that neuroblastoma in older children and adolescents has unique biology and an indolent disease course, but ultimately dismal survival. [15]

In present study there was no patient with localized disease and stage IV in more than two third of cases as compared to another study done in Morocco they had more than a third of cases of localized neuroblastoma (INSS Stage I II) In 61.1% of cases, tumors were widespread at the diagnosis, whereas 38.9% did not extend beyond the primary site. Similar is the case in HIC for the proportion of low- stage neuroblastoma as shown by data from INRG International Neuroblastoma Risk Group (30%) had low-stage (International Neuroblastoma Staging System INSS stages 1 and 2) neuroblastoma (2660/8800 cases) from 1990 to 2002.[10, 16]

Present study showed that two thirds of these neuroblastoma patients had bone marrow involvement and more than half had bony metastases at their first presentation indicating their advanced stages due to late diagnoses . High risk Neuroblastoma requires modern high-risk treatment regimens include five to six cycles of induction chemotherapy and surgery, consolidation therapy with high-dose therapy (HDT) with autologous hematopoietic stem-cell rescue and irradiation, and post consolidation therapy to treat minimal residual disease. As these regimens are not available in our center therefore these patients are inadequately treated or put on palliation as demonstrated by SIOP-PODC working group in their study. Due to the lack of transplant expertise, reduced access to blood products and pharesis, and difficulty supporting patients through the period of myelosuppression, few centers in LMIC have attempted curative treatment of high-risk neuroblastoma, and have commonly prescribed palliative care. Furthermore, the cost of isotretinoin and lack of access to monoclonal anti-GD2 antibody impede effective MRD treatment in some LMIC. [17] Neuroblastoma is one of the most difficult childhood cancers to cure with UK and Ireland 5-year survival of 64.7% for cases diagnosed. The greatest improvements were in Eastern Europe, where 5-year survival increased from 65.2% in 1999-2001, to 70.2% in 2005-07. [18] In low income countries Only a limited proportion of all children with cancer receive curative and/or palliative therapy. [19, 20]

Majority of these children in our study presented with adrenal masses along with other presentations and less than 5% had mediastinal disease as a main clinical spectrum and 7% had spinal masses presenting as paraplegia. As compared to another study done on children younger than age 21 years diagnosed with NB or ganglioneuroblastoma between 1990 and 2002 and with known primary site were identified from the International Neuroblastoma Risk Group INRG database. Patients with adrenal tumours had higher risk of events and more frequent poor prognostic clinical and biological factors (Stage IV disease, MYCN amplification, elevated serum ferritin and LDH and chromosomal aberrations) than in non-adrenal tumours (p-value=0.001). [21]

Conclusion

In resource limited settings**, n**euroblastoma stage IV is a challenging malignancy to deal with. There is intense need of increased capacity building to diagnose them early and treat in earliest possible staging for better results.

References

1. Gurney JG, Davis S, Severson RK, Fang JY. Trends in cancer incidence among children in the US. Cancer 1996; 78: 532–41
2. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. Int J Cancer1988; 42: 511–20.
3. Stiller CA, Parkin DM. International variations in the incidence of neuroblastoma. Int J Cancer. 1992; 52: 538–43
4. Magrath I, Steliarova-Foucher E, Epelman S. Paediatric cancer in low-income and middle-income countries. Lancet Oncol 2013; 14: 104 –16.
5. Brodeur GM, Maris JM. Neuroblastoma.In: Pizzo PA, Poplack DG, eds. Principles and practice of pediatric oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2002:895-938.)
6. Cohn SL, Pearson AD, London WB. The International Neuroblastoma Risk Group (INRG) classification system: An INRG Task Force report. J Clin Oncol 2009; 27:289-97.
7. Desandes E, Guissou S, Ducassou S. Neonatal Solid Tumors: Incidence and Survival in France. Pediatr Blood Cancer 2016; 63: 1375-80
8. Baker DL . Outcome after Reduced Chemotherapy for Intermediate-Risk Neuroblastoma engl j med 363; 14nejm.org: 2010 1313-23.
9. Pinto NR, Applebaum MA, Volchenboum SL. Advances in risk classification and treatment strategies for neuroblastoma. JCO 2015; 33: 3008-22
10. Bagatell R, Beck-Popovic M, London WB. Significance of MYCN Amplification in International Neuroblastoma Staging System Stage 1 and 2 Neuroblastoma: A Report from the International Neuroblastoma Risk Group Database 2009; 27:365-70
11. Hashii Y, Kusafuka T, Ohta H. A case series of children with high-risk metastatic neuroblastoma treated with a novel treatment strategy consisting of postponed primary surgery until the end of systemic chemotherapy. Pediatric Hematology and Oncology 2009; 25:5: 439-450
12. Hadley GP, Heerden JV. High-risk neuroblastoma in a sub-Saharan African country: telling it like it is. Trop Doct. 2017; 10:1177-80
13. Goodman MT, Gurney JG, Smith MA. Sympathetic nervous system tumors. In: Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995National Cancer Institute SEER Program 1999; 99:4649.
14. Meany HJ, London WB, Ambrose PF. Significance of clinical and biologic features in stage 3 neuroblastoma: A Report from the International Neuroblastoma Risk Group Project Pediatr Blood Cancer 2014; 61: 1932-39
15. Mosse YP, Deyell RJ, Berthold F. Neuroblastoma in older children, adolescents and young adults: A report from the international neuroblastoma risk group project.
16. Imane Tabyaoui I ,Tahiri-Jouti N, Serhier Z. High incidence of MYCN amplification in a Moroccan series of neuroblastic tumors. Diagn Mol Pathol 2013; 22:112–18.
17. Parikh NS, Howard SC, Chantada G. Clinical practice guidelines SIOP-PODC Adapted risk stratification and treatment guidelines: Recommendations for neuroblastoma in low- and middle-income settings. Pediatr Blood Cancer 2015; 62: 1305–16
18. Gatta G, Botta L, Rossi S. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncology 2014; 15(1):35-47
19. Magrath I, Steliarova-Foucher E, Epelman S. Paediatric cancer in low-income and middle-income countries. Lancet Oncology 2013; 14, 3: 104–16.
20. 2Balkin E M, Thompson D, and Colson KE. Physician Perspectives on Palliative Care for Children with Neuroblastoma: An International Context. Pediatr Blood Cancer 2016; 63: 872–879
21. Vo KT, Mattay KK, London WB.. Clinical, biologic, and prognostic differences on the basis of primary tumor site in neuroblastoma: A report from the international neuroblastoma risk group project. Journal of Clinical Oncology 2014;10:1621-25