Profile and Outcome of Neuroblastoma with Conventional Chemotherapy in Children Older than One year: A 15-years Experience

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ABSTRACT

The clinical profile and outcome of neuroblastoma in 103 children, older than one-year is presented. 74 had Stage IV, 27 Stage III and one patient each had Stage I or II disease. Treatment included chemotherapy followed by surgical resection/debulking. Radiotherapy was administered to those with residual tumor. Chemotherapy consisted of 'OPEC' (vincristine, cyclophosphamide, cisplatin and etoposide). The caretakers of 54 (52.4%) children either did not opt for or defaulted therapy, whilst 3 patients died before chemotherapy could be initiated. Of the remaining 46 patients, the tumor progressed during therapy in 19 (41.3%). Relapse of disease was documented in 22 (47.8%) cases. Merely 4 (8.7%) children are disease free for a period of 16.5±6.7 months. Majority of children presented with advanced disease and the outcome was dismal with conventional non-myloablative chemotherapy.

Key Words: *India, Neuroblastoma, Survival, Treatment.*

INTRODUCTION

Neuroblastoma (NBL) is the most common extracranial solid tumor in children(1). The outcome is usually favorable in infants, in whom the tumor may regress spontaneously(2). In contrast, the tumor has inconsistent response to chemotherapy in older children, often with progression or relapse after apparent remission. Recent advances in molecular genetics, megatherapy with stem cell rescue and targeted therapy have improved survival in developed nations(3-5). Reports on the outcome of children with NBL from developing countries are limited, even though pediatric oncologists manage a significant number of children with NBL(6-8). We describe patient characteristics and treatment outcome in children beyond the age of one-year with NBL. As the biological behavior of neuroblastoma in infancy is different, it is being analyzed separately.

METHODS

Previously untreated children, between the ages of 1-13 years, with an established diagnosis of NBL, were included. Case files were retrieved from the records of pediatric oncology clinic. The relevant data pertaining to diagnosis, treatment and outcome was recorded on a pre-designed proforma. Meta-iodobenzylguanidine (MIBG) scanning and MYCN amplification was not performed because of non-availability. Urinary catecholamine estimation was done in limited cases. Diagnosis of NBL was established by (*a*) fine needle aspiration cytology

with or without immunocytochemistry, or, (*b*) bone marrow examination, revealing unequivocal tumor cells in conjunction with a suprarenal mass. Staging was done according to the International Neuroblastoma Staging System(9).

The treatment included chemotherapy followed by surgical resection/debulking of the primary tumor. Children with stage I/II disease, were taken for primary surgery. Patients were administered courses of "OPEC" therapy, namely, vincristine 1.5 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 2 and etoposide 120 mg/m^2 on day 4. Hematopoietic growth factors were not administered. Response to treatment at primary/metastatic sites was reassessed after 3-5 courses. If there was no evidence of metastatic disease, resection/debulking of the primary tumor was attempted, depending on the extent and adherence of the tumor to adjoining structures. Treatment was declared unsuccessful if there was evidence of metastatic disease subsequent to 4 courses of chemotherapy. Patients with stage III or stage IV disease with residual tumor mass following surgery were administered radiotherapy to tumor bed, provided that the metastatic disease had resolved. An additional two courses of 'OPEC' were administered subsequent to local therapy.

RESULTS

In the period between January 1990 to December 2004, there were 103 children (>1 year old) with NBL. The mean age was 41.5±24.8 months (range: 12.5 months to 12.5 years). 54 (52.4%) and 41 (39.8%) children were in the age range of 1-3 and 3-6 years, respectively. Only 2 (1.9%) children were older than 9 years. The male:female ratio was 2.8:1. The salient manifestations and site of origin of primary tumor are outlined in ***Tables* I** and **II**, respectively.

Bone marrow examination could be performed in 86 children. It was infiltrated with tumor cells in 54 (62.8%). Urinary vanillylmandelic acid (VMA) levels were estimated in 10 children and were elevated in 3. Advanced Stage III or IV disease was documented in 27 and 74 cases, respectively. Localized Stage I or II disease was observed in one case each.

The treatment rendered, and outcome is described in ***Table* III**. 17 (63%) patients with Stage III and 27 (36.5%) with Stage IV disease received therapy. 17 patients received radiotherapy. Radiation dose ranged from 10-30 Gy (mean: 17.8±5.6 Gy). Tumor was found to be adherent/inoperable at the operating table in 4; all had received 4 courses of 'OPEC' prior to surgery. Treatment was declared unsuccessful in the remaining 7, as the marrow had persistent infiltration following chemotherapy.

Recurrence of tumor occurred at the metastatic and primary sites in 12 and 8 children, respectively. Relapsed disease in both primary and metastatic site was evident in 2 patients. Mean duration of interval between treatment completion and relapse was 3.9±3.2 months. All relapsed within one year and

TABLE I CLINICAL MANIFESTATIONS AT PRESENTATION (*N*=103)

Symptoms	No. (%)	Signs	No. (%)
Fever	67 (65.0)	Hepatomegaly	31 (30.0)
Abdomen lump/distension	56 (54.4)	Bone lesions	26 (25.2)
Bone pains	32 (31.0)	Splenomegaly	15 (14.6)
Proptosis	28 (27.2)	Lymphadenopathy	14 (13.6)
Lower limb paresis	2	Central nervous system metastasis	7 (6.8)
Urinary incontinence	2	Bilateral pleural effusion	4
Jaundice	3	Superior vena cava syndrome	1
Chronic diarrhea, hematuria and abnormal gait and eye movements	1 each	Opsomyoclonus and ataxia	1

The total exceeds 103, as symptoms coexisted in a single patient

TABLE II SITE OF PRIMARY TUMOR (*N*=103)

Site	No	(%)
Abdominal	87	(84.5)
Adrenal	66	
Retroperitoneal/paravertebral	13	
Too large to identify site of origin	7	
Pelvis	1	
Occult	11	(10.7)
Thorax	5	(4.8)

merely 3 relapsed later than 6 months. No patient received salvage chemotherapy or an autologous transplant.

Three patients died prior to treatment initiation. One had superior vena cava syndrome (SVCS), secondary to tumor located in the posterior mediastinum and died of respiratory failure. Another had disseminated disease with bilateral pleural effusion; the third had raised intracranial pressure secondary to metastatic brain disease. Four patients, who completed therapy, are disease free for 16.5±6.7 months. These include one child each with Stage I, II, III and IV.

DISCUSSION

More than half the patients did not receive specific treatment or defaulted therapy. Low socioeconomic background, coupled with the unfavorable outcome associated with advanced stage disease contributed to a large drop out. In addition, the assistance from non-governmental cancer support groups was restricted, and directed preferentially towards 'cancers with favorable outcomes'. The age distribution of patients has been typical(1). The male preponderance of 2.8:1, on the other hand, has been higher than figure of 1.1:1 in most large series(1). Gender bias favoring males is common in Indian society due to preferential care of male children(7,10).

The primary site could not be defined in 11 (10.7%) cases, which is higher than the textbook quoted figure of 1%(1). In 99 patients with stage IV NBL from France(11), none had an occult primary, whilst 6 (6.6%) of 91 patients reported by Kusumakumari, *et al.*(6) had an undetected primary. Greater number of patients with occult disease in our study probably reflects an insufficient investigative workup. MIBG scan was not available. CT-scan of chest/abdomen was not performed in cases with normal ultrasonography of the abdomen and X-ray of the chest. The decision was influenced primarily by non-inclination of the family towards treatment. Urinary catecholamine levels are reported to be elevated in the large majority. Merely 3 (30%) patients in the index study, on the other hand, had elevated urinary VMA levels. A lack of sensitive technique and faulty collection of sample could presumably be contributory. A non-contributory result with urinary VMA has been the experience of other centers from India as well(8,10). Of 16 infants reported from Mumbai, urinary VMA levels were elevated in 8(8).

The majority (98%), had either Stage III or IV disease. In 7 patients, the massive size of abdominal

TABLE III TREATMENT RENDERED FOLLOWING INITIAL EVALUATION AND OUTCOME

Treatment details	No. (%)
No treatment administered	44 (42.7)
Treatment default during various stages of therapy, with no meaningful assessment	10 (9.7)
Death before start of treatment due to progressive primary disease	3 (2.9)
Remaining patients available for outcome analysis	46 (44.7)
Disease progression/incomplete control during treatment	19 (41.3)
Relapse after complete treatment	22 (47.8)
Death due to sepsis	1 (2.2)
Off treatment, disease free	4 (8.7)

WHAT THIS STUDY ADDS?

- Majority of children with neuroblastoma in India present with advanced stage disease and the outcome is dismal with conventional non-myloablative chemotherapy.

disease precluded the assessment of the organ of origin. 88% patients from Malaysia, as well as Turkey, and 82% from Hong Kong had advanced Stage NBL(12-14). Delayed visit to the health care facility is presumably a factor contributing towards high proportion of patients with advanced disease. In addition, patients with localized disease are likely to be managed in surgical units, without referral to Pediatric-oncology-unit; the 'difficult' cases thus tend to get clustered.

Paraneoplastic syndrome was observed in two. One had intractable diarrhea and another had opsomyoclonus syndrome and ataxia. Patient with neurological paraneoplastic syndrome is the sole patient with Stage I disease. The lower Stage is characteristic; majority of children with this syndrome have favorable outcome with respect to their tumor(15,16). The tumor was resected completely and patient is disease free for 10-months. A single patient presented with SVCS. NBL is a rare cause of SVCS(17). Administration of 'OPEC' was uneventful and uncomplicated in the majority. Febrile neutropenia was not a limiting issue. One child died of septicemia, which was not associated with neutropenia.

The survival of patients with stage III/IV disease has been dismal. Merely 2 patients with advanced stage disease are disease free. Of the 25 patients whose bone marrow was infiltrated and followed the treatment without default, 7 (28%) had persistent infiltration following 4 courses of OPEC. Nearly, similar number of patients had disease progression/ incomplete control during therapy and relapsed after completing therapy. Majority of the relapses were observed soon after completing the therapy, indicating that the disease was suppressed temporarily by chemotherapy. The evidence is overwhelming that conventional chemotherapy was unsuccessful in controlling the disease.

Historically, the long-term survival of high-risk NBL, with non-myeloablative chemotherapy has been less than 15%(18). Kusumakumari, *et al.*(7) reported a 2-year survival of 11.7%. In a study from Turkey(13), five-year overall and event-free survival rates were 63 and 30% in Stage III, and 6 and 5%, in Stage IV patients, respectively. A 2 year disease free survival of 39% was reported in 78 patients from Malaysia (12). Myeloablative therapy with stem cell rescue and targeted therapy has improved survival in recent times(1,4,19,20). In the European Neuroblastoma Study Group, 5-year event-free survival was 38% in the melphalan-treated group and 27% in the "non-melphalan" group(4). French Society of Pediatric Oncology reported higher survival rates (83%) with high-dose chemotherapy, stem cell rescue and radiotherapy, when compared with standard treatment alone (25%), in Stage II/III disease(3). The current survival rates however remain unacceptable and have come at the expense of significant immediate and long-term morbidity(21). Information regarding MYCN status and the pathological classification for favorable/unfavorable disease is lacking in the index study. It is thus unfeasible to comment if unfavorable features were responsible for the adverse outcome.

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