PATTERN AND OUTCOME OF NEUROBLASTOMA A 10 YEAR STUDY

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Objective: *To determine the clinical pattern and outcome of children with neuroblastoma.* ***Design:*** *Retrospective analysis* ***Setting:*** *Hospital based information from the case sheets.* ***Subjects:*** *91 children with age upto 14 years treated in the Regional Cancer Center, Trivandrum. Methods: Clinical presentation, metastatic pattern and treatment outcome were analyzed* ***Results:*** *Median age of the study group was 2 5 years with a male female ratio of 1 6 1 Fifteen per cent children had early stage disease and 85% advanced disease Five children with stage III and 22 with stage IV disease did not receive any active treatment The remaining 64 children were evaluated for this analysis with a survival rate of 25% Two of the four (50%) stage I, four of the six (83.3%) stage II, five of the 18 (27 7%) stage III, three of the 32 (9%) stage IV and two of the four (50%) stage lVs patients are long term survivors* ***Conclusions:*** *Majority of the children (>80%) presented with advanced disease and outcome remained poor Only 27% of stage III and 9% of stage IV patients are long term survivors in our series. In future, approaches to detect disease at an early stage and aggressive therapeutic strategies in selected patients may improve survival*

Key words: *Neuroblastoma, Survival.*

NEUROBLASTOMA is the second JL most common solid tumor in infants and children. Prognosis for neuroblastoma varies because of its peculiar biologic behavior. The outlook for patients with limited disease which comprises—less than 25% of cases is good. However, in those with more advanced tumors or with metastasis, complex and demanding combination of surgery, chemotherapy and radiotherapy are required. Even with skilful use of these treatment modalities cure rates remain frustratingly low in most patients. We present the patient characteristics and treatment outcome of children reported to a regional cancer center during a 10 year period.

Subjects and Methods

Children up to 14 years old diagnosed as having neuroblastoma and previously untreated were included in this retrospective study. Clinical data of these children were reviewed in detail. Complete blood count, liver function tests, renal function tests, ultrasound and computerised scan of primary tumor, chest X-ray, skeletal survey, bone scan, bone marrow aspirate and

biopsy were carried out in these patients Biochemical markers like serum ferritin, serum lactic dehydrogenase and neuron specific enolase were not routinely done in these patients Even though Evan's staging system was used initially we could restage all children using medical records data according to the 1988 International Neuroblastoma Staging System (INSS) criteria(l) for this analysis

The operability was decided in each case by the surgeon Children found to be free of metastatic disease and operable, underwent surgical exploration and an attempt was made to remove as much of the tumor as possible without vital organs being sacrificed The extent of tumor resection was defined as follows complete - if no gross residual tumor remained, subtotal - if between 5% and 20% remained, partial - only if debulking is done or biopsy - if no attempt was made to resect the tumor Those who were found to have primary inoperable or inoperable tumor at laparotomy were treated with induction chemotherapy following which an attempt was made to resect the residual mass Induction chemotherapy consisted of 5 courses of Injections Vincristine (1.5 mg/m^2) Cyclophosphamide (750 mg/m^2) and Adnamycin (50 mg/m^2) Injections Cisplatin (100 mg/m^2) and Etoposide (150 mg/m^2) for 3 days were added to few patients, who could afford it, in the last 2 years of study Courses were repeated every 3 weeks If blood counts were too low subsequent courses were delayed a week Clinical evaluation was repeated after 5 courses of chemotherapy (at 4 months) Delayed/second look surgery was attempted if tumor was found to be resectable Stage III patients with residual mass after second surgery and chemotherapy received local radiation Similarly, stage IV patients whose metastatic disease responded, but with local residual disease also received radiation to primary site Patients who had complete response to initial chemotherapy and surgery were continued on same drugs for a period of one year All the four patients with stage I, four of the six patients with stage II and three of four patients with stage IVs disease were kept under follow up after surgery Two stage lib patients received chemotherapy One patient with stage IVs disease received low dose radiation for massive hepatomegaly Children who didn't achieve complete remission were considered as treatment failures

Response to therapy was evaluated using the 1988 International Criteria(l) and for those who had treatment before 1988, response to treatment was reassessed from the case records Patients were assessed periodically by physical examination, blood counts, chemistry profiles, and appropriate diagnostic imaging procedures

The study is mainly descriptive and statistical analysis had not been used since the number of patients surviving in each stage is very few

Results

Between January 1985 to December 1994, 91 patients were diagnosed to have neuroblastoma The characteristics of study population are listed in *Table I* The male female ratio was 16 1 Sixteen patients were infants and 73 were under the age of 5 years, with a median age of 2 5 years The major presenting complaints were mass and pain abdomen followed by pallor, proptosis, irregular fever and bone pain Paraparesis was seen in 5 patients, jaundice in 2 and convulsions in one case One patient presented with chronic diarrhea Abdomen was the primary site in 68 patients (adrenal in 50 and retropentoneal/abdominal in 18) According to INSS criteria, 4 patients had stage I, 6 had stage II, 23 had

stage III and 54 had stage IV, and 4 had stage IVs disease The histology was typical of neuroblastoma in 86 patients and ganglioneuroblastoma in 5 cases, of which only one subject is long-term survivor

The sites of metastatic disease are shown in *Table II* All but two patients with skeletal metastasis had bone marrow involvement Skull was the commonest site of involvement followed by femur and humerus Vertebrae were involved in three cases and pelvic bone in 2 cases One patient had involvement of lower end of radius Five patients had CNS metastatis, two patients had CNS disease at the time of diagnosis, cerebrospinal fluid cytology was positive for neuroblastoma cells in one case Three patients developed CNS disease 12, 24 and 30 months after initiation of therapy One stage IV patient developed bilateral testicular metastasis 5 months after diagnosis

Five children with stage III and 22 with stage IV disease did not receive any active treatment due to parental refusal The outcome of the remaining 64 evaluable children who had complete definitive treatment is shown m *Table III* Out of the fourteen patients with low stage disease *(i.e.* with stages I, II and IVs), eight (571%) patients are alive, free of disease with a median survival of 46 months.

The type of primary surgical resection

TABLE I–*Characteristics of Study Population*

Feature	No.	(%)
Total	91	
Sex		
Male : Female	56:35	
Age (yr)		
1	16	17.6
1-2	19	20.8
2-5	38	41.8
> 5	18	19.8
Median age (yr)	2.5	
Site of primary tumor		
Adrenal	50	54.9
Retroperitoneal/ Abdominal	18	19.8
Thorax	3	3.2
Pelvis	2	2.2
Dumb bell tumor	5	5.5
Cervical	2	2.2
Olfactory	3	3.2
Nasopharynx	2	2.2
Unknown	6	6.6
INSS Stage		
I	4	4.4
II*a*	4	4.4
II*b*	2	2.2
III	23	25.3
IV	54	59.3
IVs	4	4.4

TABLE II–*Metastatic Pattern in Neuroblastoma*

Site	No
Bone marrow	**35**
Bone	**28**
Liver	**13**
Distant lymph node	**11**
Central nervous system	**5**
Testis	1

TABLE III–*Survival of 64 Patients with Neuroblastoma Treated During 1984-1994.*

Stage	No. of evaluable patients	Survivors	(%)
I	4	2	(50.0)
II	6	4	(83.3)
III	18	5	(27.7)
IV	32	3	(9.0)
IVs	4	2	(50.0)
Total	64	16	(25.0)

in fifty patients with advanced disease (stages III and IV) is given in *Table IV* Of the twenty three patients with stage III disease, only eighteen were evaluable for treatment results Of the eighteen evaluable patients m stage III, surgical resection consisted of subtotal resection in one patient, paitial resection in nine patients and biopsy in eight patients All the eighteen patients received chemotherapy with Vincristine, Adriamycin and Cyclophosphamide Three patients underwent complete excision of primary tumor after chemotherapy Five patients received radiation for local control of tumor Eight patients achieved complete remission after surgery, chemotherapy and radiotherapy Seven patients achieved partial remission and no response was seen in three patients Of the eight patients with complete remission, five patients are alive free of disease (28%) at 36 months to 108 months (median survival 42 months) Two patients developed distant metastasis and one patient died of hepatitis

Complete surgical resection was done in one of the thirty two evaluable stage IV patients All others had biopsy as the primary form of surgical management Complete excision of the primary was done in three cases after chemotherapy Of the thirty two evaluable patients, twenty four received Vincristine, Adriamycin and Cyclophosphamide and eight patients received Cisplatin and Etoposide in addition Three patients received radiation to local site Complete remission was attained in six patients of which three patients subsequently relapsed, two in CNS and one in primary site Three patients are alive well with a median follow up of 36 months

TABLE IV–*Type of Surgical Resection of Primary Tumor in 50 Children with Stages III & IV Neuroblastoma*

Procedure	No
Complete Resection	
At diagnosis	3
Delayed operation	3
Second look	2
Total	8
Partial Resection	
At diagnosis	9
Delayed surgery	0
Second look	1
Total	10
Biopsy only	32
Total	50

There were sixteen patients below one year of age in this series Of the 16 patients one had stage I disease, four had stage II, one had stage III, six had stage IV and four had stage IV-S disease None of the patient with stage IV received any treatment because of parental refusal One stage III and one stage IV-S patient received chemotherapy with Vincristine, Cyclophosphamide and Adriamycin One stage IV-S patient with massive hepatomegaly received low dose hepatic irradiation Two patients in stage IV-S and one stage HI patient developed recurrence (8m, 8m and 48m) Seven patients are alive well with a median follow up of 70 mo (62 mo-104 mo).

Myelotoxicity was not significant with Vincristine, Adriamycin and Cyclophosphamide There were 11 episodes of grade 3-4 neturopenia in patients who received the 5 drug combination. There were five admissions with febrile neutropenia. No episode of septicemia was encountered One child died of hepatitis infection.

Discussion

Neuroblastoma constitutes about 5 8% of all childhood malignancies seen at our center. The clinical features like age, stage and site of primary tumor were similar to

many reported series(2), with 85% of patients in an advanced stage at the time of diagnosis (stages III and IV) Metastatic sites, included bone marrow/bone, lymph nodes, liver, central nervous system (CNS) and testis Previously subjects with neuroblastoma were not considered to be at risk for the development of mtracranial disease but aggressive chemotherapy in addition to increasing survival has resulted indirectly in relapses at sites like the CNS and testis(3,4)

The prognosis for neuroblastoma varies because of its peculiar biologic behavior and it is often difficult to compare results of survival because of marked differences in respective staging systems Even though Evans' staging system was used initially, we could restage all these patients according to 1988 INSS criteria(l) Surgical resection alonme is sufficient for many children with stage I, II and stage IV-s tumors (5,6,14) Metastatic disease is rarely curable even with high dose chemotherapy followed by bone marrow transplantation(7,8) Patients with locally advanced disease (stage III) appears to be a heterogenous group with survival rates varying between 40-70%(9-12) Prognosis is favorable for infants < 1 year of age even if the tumor is in an advanced stage(13)

Several investigators have reported the effectiveness of aggressive surgery and chemotherapy for locally advanced neuroblastoma(14,15) Gross total resection has improved survival in patients with non-metastatic neruoblastoma But the role of surgery in stage IV patients is less clear, it may be important if metastatic sites have completely responded to systemic theiapy The optimal time of surgical resection is uncertain Shamberger *et al* in their study concluded that surgical resection of stage III and IV tumois is safer after initial chemotherapy(16) Resection of the tumor from aorta and neighboring blood vessles was easier after chemotherapy, but this didn't affect the long term survival Complete surgical resection was found to be an important prognostic factor in a series(9) Complete tumor resection was possible m 63% of cases and the survival rate of patients with complete resection was significantly different from those with partial resection (68% vs 20%)(9)

The importance of achieving a complete clinical response to chemotherapy in widespread disease has been previously demonstrated^) Evans *et al* reported a 44% disease free survival using a combination of Vincristine, Cyclophosphamide and DTIC(6) The disease free survival was 76% m a group of 14 stage IV patients treated with Cyclophosphamide, Cisplatin, Teni-poside, Doxorubicin and DTIC(17) West *et al* used intensive chemotherapy (MADDOC) in 25 Evans' stage III patients, the event free survival (EFS) was 72% with a median follow up of 85 mo(10) Recently, Kushner *et al* reported that cytotoxic therapy can be avoided in nonstage IV patients without N-myc amplification(18).

The role of radiation in controlling local disease is controversial Castleberry *et al* in a randomized trial used chemotherapy with or without radiotherapy(19) Complete response (76% vs 46%) and overall survival (73% vs 41%) were better in the group receiving radiation, but the pattern of failure was nearly identical in the two arms.

Survival rates in our series were low as compared to these reports. The number of patients having low stage disease was small and this might have influenced the percentage of survival m this group. Aggressive treatment modalities were not used in advanced stage disease. Only eight patients had complete excision of the tu-

mor (primary and second look) Majority of the patients (42 cases) received Vincristine, Cyclophosphamide and Adriamycin Only eight patients received Cisplatin and Etoposide in addition The duration of survival was more in those patients who received Cisplatin/Etoposide compared to those who didn't (12 mo vs 6 mo) Only clinical factors were taken into consideration for defining therapy in this study None of the biological factors were routinely analyzed in these tumors

A number of clinical and biological prognostic factors for neuroblastoma has been identified(20-24) These include age, stage, histopathology biochemical markers, N-myc amplification in tumor cells, tumor ploidy, chromosomal abnormality, TRKA expression m tumor cells and *in vitro* growth of the tumor cells in culture N-myc amplification can be an important predictor of outcome in neuroblastoma but its presence or absence does not identify all patients who are destined to fail therapy Combined data from numerous groups indicate that as many as 20 to 40% of stage III neuroblastoma patients without N-myc amplification will ultimately fail therapy

We conclude that combined modality treatment with aggressive surgery and intensive chemotherapy is needed to cure majority of neuroblastoma patients older than 1 year of age who present in an advanced stage The less aggressive treatment approach has resulted in a poor outcome in our study In order to get better survival rates, adapting therapeutic strategies according to the risk group is very important Patients must be categorized according to their risk group based on precise clinical and biological factors at diagnosis such as age, stage, histopathology, DNA ploidy, tumor cytogenetics and N-myc amplification This approach will help to find out groups of patients who require no therapy where a spontaneous regression is expected, those whose tumors are curable with intensive treatment and those who have little chance of cure even with aggressive chemotherapy and bone marrow transplantation

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