PRESENTING FEATURES AND TREATMENT OUTCOME OF 78 MALAYSIAN CHILDREN WITH NEUROBLASTOMA

Ng Sze Mag, Wan Ariffin Abdullah, Lin Hai Peng and Chan Lee Lee

Department of Pediatrics, University Hospital, 59100 Kuala Lumpur, Malaysia

Abstract. To study the distribution of presenting features and their prognostic significance in neuroblastoma treated in a single institution in Malaysia. A retrospective study was made of 78 neuroblastoma cases diagnosed and treated in the University Hospital, Kuala Lumpur, Malaysia between June 1982 and February 1997. Diagnosis was established by standard histological criteria. The presenting features were evaluated for their distribution and prognostic influence. Disease-free survival from diagnosis was the outcome variable of interest. The ages ranged from 0.1 to 11 years old (median: 3 years old). The tumor originated from the adrenal glands in 83% and the majority of cases presented in advanced stage (stage III 22%, stage IV 66%). Bone marrow was the commonest site of distant metastasis occurring in 45% of patients. The main presenting signs and symptoms in decreasing order were pallor, fever, abdominal mass, weight loss, and bone/joint pain. Univariate analysis conferred age, initial stage and Hb level as significant prognostic factors. No influence in disease-free survival was found for sex, race, primary site, urinary vanillylmandelic acid level, white cell count and platelet count. Overall 2-year disease-free survival was achieved in 27 (39%) patients. Four patients underwent bone marrow transplant, three of whom achieved 2-year disease-free survival. The results suggest that age, initial stage and hemoglobin level are significant prognostic factors based on univariate analysis. In addition, more Malaysian children presented with adrenal primary site and advanced disease compared to previous reported studies.

INTRODUCTION

Neuroblastoma is the most common solid extracranial tumour in childhood (Berthold *et al,* 1994; Joshi *et al,* 1992). It has an annual incidence of 9 cases per million (Joshi *et al,* 1992) and it accounts for 11% of all deaths from childhood cancer. It constitutes 8% to 10% of childhood malignancies and 50% of neonatal malignancies (Angstman *et al,* 1990), although in Peninsular Malaysia, the incidence of neuroblastoma is 6.1% of all childhood malignancies (Lin *et al,* 1995). Various clinical and biological features have been reported in an attempt to determine prognostic significance. However, the estimation of prognosis for children with neuroblastoma is difficult due to the wide range of outcomes, different therapies and side effects of treatment in small children (Evan *et al,* 1987).

We report the presenting features and treatment outcome of 78 Malaysian children diagnosed with neuroblastoma and treated in the University Hospital, Kuala Lumpur, Malaysia, one of four major pediatric cancer centers in Malaysia. The aim of the study is to evaluate the distribution of various presenting features and to identify their prognostic significance among the Malaysian population.

Correspondence : Dr Ng Sze May, c/o Human Resource Department/Ms Tina Dresser, Royal Hobart Hospital, GPO Box 1061L, Hobart, Tasmania 7001 Australia.
Tel : 041-2437273; Fax : (03) 6231198 E-mail : ngezemay@hotmail.com

MATERIALS AND METHODS

Patients

The sample of the study included 78 pediatric patients (≤12 years of age) with newly diagnosed neuroblastoma admitted to the University Hospital, Kuala Lumpur, Malaysia between June 1, 1982 to February 2, 1997. In all patients, the diagnosis was based on tissue biopsy specimen of either primary or metastatic lesions, and/or elevated vanillylmandelic acid with bone marrow aspirate containing malignant cells. Ages at diagnosis ranged from 0.1 to 11 years old, with the median age as 3.0 years old and mean age as 3.3 years old. Patients were staged according to the Evan's criteria based on X-rays, bone scans, CT scans, bone marrow aspirates and/or trephine biopsies Evans *et al,* 1984).

The following variables were investigated for their distribution and prognostic influence on treatment outcome: age, sex, race, primary site, initial stage, initial urinary VMA level, WCC, Hb level and platelet count. Studies on N-myc amplification,

1p deletion, Shimada histological classification and lactate dehydrogenase level were not done due to inadequate facilities. Influence of serum ferritin was not analysed as only a few patients had serum ferritin investigations routinely done. Disease-free survival from diagnosis was the outcome variable of interest.

Treatment

As initial treatment, all patients received either 6 courses of OPEC (oncovin, cisplatinum, etoposide and cyclophosphamide) or ACVD (adriamycin, cyclophosphamide, vincristine and dactinomycin) alternating 3 weekly with PCVm (cisplatinum, cyclophosphamide, vincristine and Vm26). Assessment was done after 2 courses. Patients with no response or progressive disease were either given second line chemotherapy with VETOPEC (vincristine, etoposide and cyclophosphamide), or palliation with either VAC (vincristine, actinomycin and cyclophosphamide) or oral melphalan, with or without radiotherapy.

All patients underwent surgery. Radiotherapy was given for residual disease following chemotherapy and surgery. Maintenance therapy with cyclophosphamide and incristine were given for a year in patients with advanced disease who had achieved remission. Four patients with stage IV disease had bone marrow transplants at 14 months, 15 months, 18 months after date of diagnosis, with conditioning using melphalan for autologous transplant (1 case), and adriamycin, carboplatin and melphalan for allogenic transplant (3 cases).

Statistical methods

The relationship of each presenting feature to 2-year disease-free survival was adjusted univariately by the Pearson chi-square statistics for categorical variables. Test statistics for comparison analyses were regarded as significant if the p-value was less than 0.05. Disease-free survival was calculated from the date of diagnosis to the date of last follow-up or date of death or relapse. Patients lost to follow-up were excluded. Life-table analysis for overall 2-year disease-free survival was calculated using the Kaplan-Meier method. Comparison of survival between groups of patients were performed using the log-rank test.

RESULTS

The ages ranged from 0.1 to 11 years old. The mean age at diagnosis was 3.3 years old and the median age was 3 years old. The distribution of presenting features are shown in Table 1. Patients below 4 years old comprised of 78% of all cases and 95% of patients were below 8 years old. The majority of cases presented were stage IV (66%) and stage III (22%). There were no stage I cases in the study.

Sites of distant metastasis at diagnosis are shown in Table 2. The bone marrow was the commonest site of metastasis. The most common location of metastatic bony lesion in order of decreasing frequency being the long bones, skull and ribs. Orbital metastasis refer to involvement of the soft tissues of the orbit. There was evidence of intraspinal extension in 3% of patients.

The main presenting symptoms and signs are listed in Table 3. At initial presentation, the commonest features were pallor, fever and abdominal mass. Weight loss was reported in 36% and bone or joint pain in 33% of patients. Other presenting symptoms or signs were bleeding, infection or sepsis, seventh nerve palsy and bilateral leg swelling.

Table 4 demonstrates univariate analysis of presenting features and their influence on 2-year disease-free survival. Age exhibited an influence on disease-free survival. Infants less than a year old had a significantly better prognosis compared to children 1 to 12 years old ($p = 0.03$). Initial stage at diagnosis was also a significant prognostic factor ($p = 0.03$). Our univariate analysis also showed that low Hb level had unfavorable prognostic impact ($p = 0.04$). No influence in disease-free survival was found for the following variables: sex, race, primary site, urinary VMA level, WCC and platelet count.

The overall 2-year disease-free survival was achieved in 27 (39%) patients. Ten patients were lost to follow-up and were not included in the survival analysis. Four patients who presented with stage IV disease had bone marrow transplant. Three of these patients (75%) achieved 2-year disease-free survival.

DISCUSSION

In this study, we have shown that age, initial stage and Hb level emerged as significant prognostic factors based on univariate analyses. Notably, sex, race, primary site, urinary VMA level, WCC and platelet count did not show any significant effect on treatment outcome. The relationship of initial stage to prognosis has been firmly established

Table 1
Distribution of presenting features on 78 neuroblastoma cases.

Features	Category	No. of patients	%
Age (years)	0-2	36	47
	2-4	24	31
	4-6	7	9
	6-8	6	8
	8-10	3	4
	10-12	1	1
Sex	Male	34	44
	Female	44	56
Race	Malay	28	36
	Chinese	45	58
	Indian	4	5
	Other	1	1
Primary site	Adrenal	63	88
	Paravertebral	6	8
	Intrarenal	1	1
	Undetemnined	2	3
Initial stage (Evans criteria)	I	0	0
	II	2	2
	III	16	22
	IV	49	66
	IVs	7	10
Urinary VMA level	Normal	13	20
	Elevated	52	80
WCC (x 10^9/l)	≤ 5	12	17
	> 5	58	83
Hb level (g/dl)	≤ 10	49	71
	> 10	20	29
Platelet count (x 10^9/l)	≤ 150	21	32
	> 150	45	68

Data not available for some patients
VMA = Vannillylmandelic acid; WCC = white cell count; Hb = hemoglobin

Table 2
Site of distant metastasis of 78 neuroblastoma cases.

Initial metastasis spread	No. of patients	%
Bone Marrow	35	45
Lymph nodes	27	35
Bone	27	35
Liver	20	26
Orbitals	12	15
Lungs/pleura	8	10
Skin	4	5
Intracranial	3	4

Data not available for some patients

Table 3
Main presenting symptoms and signs of 78 neuroblastoma cases.

Variable	No. of patients	%
Pallor	44	56
Fever	43	55
Abdominal mass	41	53
Weight loss	28	36
Bone/joint pain	26	33
Bleeding	3	4
Infection/sepsis	2	3
7^{th} nerve palsy	2	3
Leg swelling	2	3

Data not available for some patients

Table 4
Distribution and incidence of presenting features on treatment outcome.

Features	Category	No. of patients	2-year disease-free survival	(%)	p-value
Age (years)	< 1	14	9	(64)	0.03
	≥ 1	55	18	(33)	
Sex	Male	29	10	(34)	0.50
	Female	40	17	(43)	
Race	Malay	23	7	(30)	0.21
	Chinese	42	20	(48)	
	Indian	3	0	(0)	
	Other	1	0	(0)	
Primary site	Adrenal	63	29	(46)	0.13
	Paravertebral	6	4	(66)	
	Intrarenal	1	0	(0)	
	Undetermined	2	1	(50)	
Initial stage	I	0	0	(0)	0.03
	II	2	2	(100)	
	III	12	5	(50)	
	IV	44[a]	12[b]	(27)	
	IVs	7	5	(71)	
UrinaryVMA level	Normal	10	2	(20)	0.18
	Elevated	49	21	(43)	
WCC(x 10^9/l)	≤ 5	11	2	(18)	0.16
	> 5	52	21	(40)	
Hb level (g/dl)	≤ 10	42	17	(40)	0.04
	> 10	19	14	(74)	
Platelet count (x 10^9/l)	≤ 150	20	6	(30)	0.23
	> 150	39	18	(46)	

Data not available for some patients
[a] Include 4 patients who underwent BMT
[b] Include 3 BMT patients
VMA = Vannillylmandelic acid; WCC = white cell count; Hb = hemoglobin

in many studies of neuroblastoma (Berthold *et al*, 1994; Evans *et al*, 1987) and was confirmed in this study (p = 0.03). Only 27% of stage IV patients achieved disease-free servival compared to 100% in stage II, 50% in stage III and 71% in stage IVs. These results were comparable to previous reported studies (Joshi *et al*, 1992; Angstman *et al*, 1990).

Studies have shown that 50% of neuroblastoma tumors occur in children under age 2 years and 75% of the tumor occur in children under age 4 years (Angstman *et al*, 1990; Evans *et al*, 1987). This is similar to our study which showed 47% of all patients were under 2 years and 78% were under 4 years old. In many studies, age at diagnosis has been found to have significant prognostic value, being inversely proportional to treatment outcome and irrespective of disease stage (Joshi *et al*, 1992; Machin, 1982; Oppedal *et al*, 1988; Jereb *et al*, 1984). In our study, infants less than one year old had a significantly better treatment outcome compared to children ≥ 1 year old (p = 0.03). The reason for the marked difference in treatment outcome between infants and children is not clear. The poor outcome in older children may be related to the concomitant occurrence of other poor prognostic factors, for example a greater proportion of stage IVs, N-myc amplification and lp deletion within the age group (Carlson, 1988).

Similarly, a low Hb level of ≤ 10g/dl was significantly associated with a poor treatment outcome ($p = 0.04$). The poor outcome may be related to bone marrow involvement in the disease and therefore to stage. As such, it is felt that it should be deemphasised as a prognostic feature.

These findings were based on univariate and stage irrespective analysis. As such, these factors may likely be associated with each other and therefore not truly independent. Due to our small sample size, multivariate analysis was not done.

The male to female ratio of incidence was 1: 1.3 but the difference between the two groups in their 2-year disease-free survival was not significant ($p = 0.50$). The latter findings are in agreement with earlier studies by Berthold *et al* (1994) and Evans *et al* (1987). However, Pritchard and Kemshead (1983) and Kinnier-Wilson and Drapor (1974) found that males had a greater tendency to be at a more advanced stage compared to females and therefore, were more likely to have a poorer prognosis.

Our study also showed that the adrenal gland constituted 88% of all primary tumor sites. This is comparably higher than previous reported studies of 50% to 70% (Evans *et al,* 1987, 1984). Our findings showed that the primary site of the tumor was not a significant prognostic factor ($p = 0.13$). Our results contrast with Massad *et al* (1996) who found that the site of the primary tumor was an independent variable affecting survival. The abdominal sympathetic chain primary site was found to have the worst prognosis, followed by the adrenal primary site (Angstman *et al,* 1990).

Limitations of this study include a small sample size, treatment variability and lack of biologic markers such as N-myc amplification, 1 p deletion, Shimada classification, lactate dehydrogenase and ferritin levels, which may influence treatment outcome and prognostic factors. Additional studies are therefore needed to further evaluate the prognostic factors of neuroblastoma in this population.

The overall 2-year disease-free survival of 39% achieved in the Malaysian population is slightly higher compared to other studies which reported a 2-year survival of 30% to 35% (Angstman *et al,* 1990). This may be contributed by the high survival of bone marrow transplant patients.

Thus, this single institution study shows that more Malaysian children with neuroblastoma presented with adrenal primary site and advanced disease compared to Western children. However, the treatment outcome was similar. Univariate analyses also showed that age, initial stage and Hb level were significant prognostic factors.

REFFERENCES

Angstman KB, Miser JS, Franz II WB. Neuroblastoma. *Pract Therapeutics* 1990; 41: 238-44.

Berthold F, Kassenbohmer R, Zieschang J. Multivariate evaluation of prognostic factors in localized neuroblastoma. *Am J Pediatr Hematol Oncol* 1994; 16: 107-15.

Carlson N. Why age has independent prognostic significance in neuroblastomas: Evidence of intrauterine development and implications for the treatment of the disease. *Anticancer Res* 1988; 8: 255-62.

Evans AE, D'Angio GJ, Propert K, Anderson J, Hann HL. Prognostic factors in neuroblastoma. *Cancer,* 1987; 59: 853-59.

Evans AE, D'Angio GJ, Randolph J. A proposed staging for children with neuroblastoma. *J Clin Oncol* 1984; 2: 799-803.

Jereb B, Bretsky SS, Vogel R, Helson L. Age and prognosis in neuroblastoma: Review of 112 patients younger than 2 years. *J Pediatr Hematol Oncol* 1984; 6: 223-43.

Joshi VJ, Cantor AB, Altshuler G, *et al.* Age-linked prognostic categorization based on a new histologic grading system of neuroblastomas. A clinicopathologic study of 211 cases from the pediatric oncology group. *Cancer* 1992; 15: 2197-209.

Kinnier-Wilson LM, Draper GJ. Neuroblastoma, its natural history and prognosis: A study of 487 cases. *Br Med J* 1974; 3: 301-9.

Lin HP, Khuzaiah R, Hoe T. Epidemiology of childhood cancer in Malaysia in 1993. *Proc Am Soc Clin Oncol* 1995; 14: 186.

Machin G. Histogenesis and histopathology of neuroblastoma. In: Pochely C, ed. Neuroblastoma: Clinical and biological manifestations. New York: Elsevier Biomedical. 1982; 194-231.

Massad M, Slim MS, Mansour A, Darbous I, Firzli S, Issa P. Neuroblastoma: Report on a 21-year experience. *J Pediatr Surg* 1996; 2: 388-91.

Oppedal BR, Storm-Mathisen I, Lie SO, Brandstzaeg P. Prognostic factors in neuroblastoma: Clinical, histopathological and immunohistochemical features and DNA ploidy in relation to prognosis. *Cancer* 1988; 62: 772-80.

Pritchard J, Kemshead J. Neuroblastoma: Recent developments in assessment and management. *Rec Results Cancer Res* 1983; 88: 69-78.