Outcome of children older than one year with neuroblastoma

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ABSTRACT

الهدف: دراسة المحصلة الشفائية للمرضى المصابين بالورم الجذعي العصبى في الفئة العمرية أكبر من عام بمدينة الملك عبد العزيز الطبية بجدة.

الطريقة: بأثر رجعي قمنا بمراجعة الخصائص السريرية بالملفات الطبية لـ ٥٢ مريض مصاب بالورم الجذعي العصبي الذين تم علاجهم في الفترة الزمنية من سبتمبر ١٩٨٧ حتى مايو ٢٠٠٣. عولج هؤلاء المرضى بالعلاج الكيميائيOPEC المكون من Vincristine، Cisplatin، Etoposide and Cyclophosphamide) أو OPEC/OJEC Carboplatin عوضاً عن Cisplatin والتدخل الجراحي بالإضافة للعلاج الشعاعي في بعض الحالات. ٣ مرضى تلقوا علاج جراحي فقط. لم يجرى لأى مريض نقل نخاع العظم.

النتائج: ٢٥ مريض من الذكور متوسط العمر لهؤلاء المرضى١,٢. ٣٤ مريض(٦٥٪) في المرحلة الرابعة و١٢ (٢٣٪) في المرحلة الثالثة و٦ مرضى (١١٪) في المرحلة الثانية.الورم المبدئي كان في البطن في ٧٠٪ من الحالات. ٣ مرضى من المرحلة الثانية عولجوا بالتدخل الجراحي فقط، الثلاثه الأخرين احتاجوا علاج كيميائي، جميعهم أحياء ولم ينتكس المرض لديهم.جميع مرضى المرحلة الثالثة والرابعة تلقوا العلاج الكيميائي بالإضافه للتدخل الجراحي والعلاج الأشعاعي في بعض الحالات. بعد إعطاء الجرعات الأولية ١٧ مريض (٣٢٪) كانت استجابتهم كاملة و١٠ مرضى(١٩٪) كانت استجابتهم جزئية. ٦ مرضى (١٢٪) توفوا نتيجة للتأثيرات الجانبية للعلاج الكيميائي.أمكن إجراء استئصال جراحي كامل لـ١١ مريض (٢٢٪) واستئصال جزئي لـ ١٥ مريض (٣٠٪). تطور المرض أو انتكاسته حدث لـ ٢٧ مريض (٥١٪). خلال متوسط فترة متابعة ٢٤ شهر(٤–١٢٠) كانت محصلة عدم انتكاس المرض خلال سنتين ١٠٪،٨٢٪و٨٧٪ والمحصلة الشفائية ١٢٪،٨٣٪و ١٠٠٪ لعلاج المرحلة٤، ٣ و٢ على التوالى.

خاتمة: كانت المحصلة الشفائية لعلاج الورم الجذعي العصبى الموضعي للأطفال من الفئة العمرية اكبر من سنة جيدة عند مقارنته بالمرحلة الرابعة. نقل النخاع العظمي بالإضافة لجرعات علاجية عالية قد تحسن نتيجة العلاج فى النوع الأخير. التاثيرات الجانبية كانت ملحوظه وتوجية العلاج حسب عوامل الخطر قد ينقص من هذه التاثيرات.

Objectives: To assess the outcome of children older than one year with neuroblastoma treated at King Abdul-Aziz Medical City, Jeddah, Kingdom of Saudi Arabia.

Methods: We retrospectively reviewed the files of 52 children older than one year with neuroblastoma (NBL) treated at our center between September 1987 and May 2003. Treatment consisted of OPEC chemotherapy regimen (vincristine, cisplatin, etoposide, and cyclophosphamide) or alternating OPEC/OJEC (carboplatin in place of cisplatin), surgical resection ± radiotherapy (RT). No patient received high dose therapy (HDT).

Results: Thirty-four patients (65%) were stage 4, 12 (23%) stage 3, and 6 (11%) stage 2. Three stage 2 patients were treated with surgery only, all are alive in complete remission (CR). All stage 3 and 4 patients were treated with chemotherapy and surgery ± RT. After induction chemotherapy, CR was achieved in 17 patients (32%) and partial remission in 10 (19%). Complete surgical resection was possible in 11 patients (22%). Disease recurrence or progression occurred in 27 patients (51%). With a median follow-up of 24 months (range 4-120), the 2-year event free survival was 10%, 82%, and 87% and the overall survival was 12%, 83%, and 100% for stage 4, 3, and 2.

Conclusions: Children older than one year with localized NBL have good prognosis compared to those with stage 4. The use of HDT may improve the outcome in the latter group. Toxicity was significant, and adoption of risk-stratified treatment may help to reduce treatment complications.

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Neuroblastoma (NBL) is the most common extracranial childhood tumor.[1] The prognosis of NBL is dependent on the stage of tumor and age of the patient at diagnosis.[2] Biological variables such as N-myc amplification and others are important prognostic factors.[3] Children older than one year with metastatic NBL and poor biological marker(s) have a poor outcome.[4] Efforts to improve survival of patients with NBL focused on identification of risk groups based on clinical and biologic variables.[4,5] Children older than one year with stage 4 NBL constitute the majority of the high risk category. The use of intensive chemotherapy, surgery with or without radiotherapy (RT), and high-dose therapy (HDT) with stem cell transplantation is now recommended in high risk patients.[6,7] In this study, we review the results of children older than one year with NBL to assess the outcome and causes of treatment failure.

Methods. We retrospectively reviewed the clinical data of 52 children older than one year with NBL treated at King Abdul-Aziz Medical City, Jeddah, Saudi Arabia between September 1987 and May 2003. Local ethical approval was obtained prior to commencement of the study. The primary tumor was evaluated by ultrasound, CT or MRI scan at presentation. Urinary vanillylmandelic acid (VMA), homovanillic acid (HVA), and dopamine were determined whenever possible. Staging investigations included bilateral bone marrow aspirations and trephines, 123-iodine-metaiodobenzylguanidine (MIBG) scintigraphy or Technetium-99m bone scan. There are no facilities to carry out N-myc or other biological studies. Three patients did not receive chemotherapy. Twenty-five patients received OPEC chemotherapy regimen (vincristine, cisplatin, etoposide, and cyclophosphamide) and 24 received alternating OPEC/OJEC (carboplatin in place of cisplatin) given on a 3 weekly basis depending on absolute neutrophil count (ANC) -1.0×10^9/L and a platelet count -100 × 10^9/L.[8,9] No patient received high dose therapy. Eight patients with stage 4 NBL, and 4 with stage 3 received 13-Cis-retinoic acid.[8] Diethylene Triamine Penta Acetic acid and audiometry were performed every 3 courses and treatment was adjusted if necessary according to protocol guidelines.[9,10] Response was defined as complete remission (CR) if there is no visible tumor, very good partial remission (VGPR) when the primary tumor decreased by 90-99% and no metastatic tumor, and partial remission (PR) if there is more than 50% reduction in primary and metastatic tumor. The response was assessed after 2 and 4 cycles of chemotherapy and surgical resection of residual primary tumor was attempted after achieving metastatic CR in stage 4 patients and in patients with localized tumor when resectability was thought to be feasible. Granulocyte colony-stimulating factor (G-CSF) 5 µg/kg/day was optional in severely neutropenic patients with documented infection. Platelet transfusions were given to maintain a platelet count above 10 x 10^9/L in nonfebrile patients and above 20 × 10^9/L in the presence of fever. Packed red blood cells were given as clinically indicated and to keep the hemoglobin level over 8 g/dL. All patients received trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis carinii*.

Results. There were 25 boys, and ages ranged from 1.5-10 years (median 2.1). The patients' characteristics are shown in **Table 1**. Three patients with localized NBL were treated with surgery only and the toxicity data of 7 patients were missing. Seventeen patients (40%) developed severe hematological, infectious, and other complications. Six died of chemotherapy toxicity, 4 with gram negative septicemia, one with septic shock and negative blood culture and one with interstitial pneumonitis. Five needed modification of their chemotherapy because of hemorrhagic cystitis (n=1), hearing loss and nephrotoxicity (n=2), and 2 patients developed peripheral neuropathy and paralytic ileus. In the remaining 6 patients, chemotherapy was completed with no significant modification. Seven (20%) patients with stage 4 NBL did not complete chemotherapy and died of progressive disease, and 3 died of toxicity during

Table 1 - Patients' characteristics.

Clinical features	Patients (n=52) n (%)
Gender	
Male	25 (48)
Female	27 (52)
Age at diagnosis	
1-2 years	10 (19)
>2-5 years	38 (73)
>5 years	4 (7)
Stage	
1	0
2	6 (11)
3	12 (23)
4	34 (65)
Site of primary	
Abdomen	34 (65)
Thorax (±abdomen)	10 (19)
Others	8 (15)
Shimada unfavorable[11]	15/40

data lacking for 12 patients

induction chemotherapy. Five achieved CR/VGPR and 8 achieved PR. No assessment data are available for the remaining 11 patients. Patients with stage 2 and 3 responded well to induction chemotherapy. Details of response of all patients are shown in **Table 2**. Seven (20%) with stage 4 relapsed after finishing treatment. All died except one who was 13 months at initial diagnosis and developed local relapse 12 months later. He is alive with residual tumor at the site of the primary. Only one (8%) patient with stage 3 relapsed locally 19 months after primary diagnosis. He remains alive and well after second line chemotherapy, surgical resection, and local radiotherapy. The overall results showed that 17/49 (34%) achieved CR/VGPR, 10 (20%) PR, and 8 (16%) showed no response (n=1) or progressive disease (n=7). Six patients (12%) died of toxicity (no available data for remaining 11 patients). At the end of induction chemotherapy, 24 patients had undergone complete (n=11) or partial (n=15) surgical resection of the primary tumor. Six patients received 2-3 additional cycles of chemotherapy before surgery. **Table 3** shows the details of the surgical treatment. Eight patients with residual tumor received local radiotherapy and 13-Cis-retinoic acid. With a median follow-up of 24 months (range 4-120), the 2-year event free survival (EFS) was 10%, 82%, and 87% and the overall survival (OS) was 12%, 83%, and 100% for stage 4, 3, and 2 (**Figure 1**).

Table 2 - Tumor response after induction chemotherapy.

Stage	No data	CR/VGPR	PR	NR/PD	Relapse
4	11/34	5/20 (25%)	8/20 (40%)	7/20 (35%)	7
3	0	9/12 (75%)	2/12 (16%)	1/12 (9%)	1
2	0	3	0	0	1
Total	**11**	**17/49 (35%)**	**10/49 (20%)**	**8/49 (16%)**	**9**

CR - complete remission, VGPR - very good partial remission, PR - partial remission, PD - progressive disease

Table 3 - Details of surgical intervention.

Surgical resection	Stage 2 (n=6)	Stage 3 (n=12)	Stage 4 (n=34)
Primary resection	3	0	1
Complete excision	3	6	2
Partial excision		5	10
Biopsy		1	18

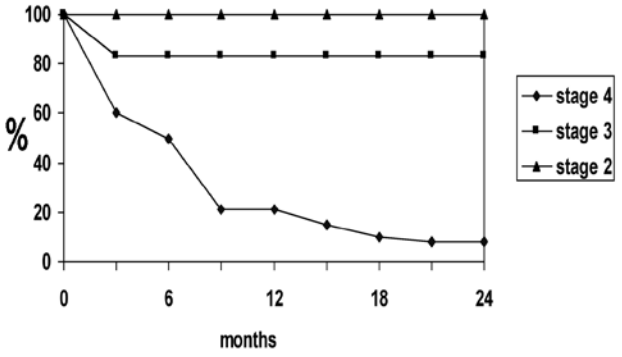

Figure 1 - Overall survival.

Discussion. In children with NBL, the age of the child and stage of tumor at initial presentation and biological characteristics of the tumor such as N-myc amplification are the most important factors that affect outcome.[2-4] Clinical, biological, and other features are currently used to stratify patients into different risk groups. This helps to deliver risk-tailored treatment and reduces morbidity and mortality without compromising outcome.[11-14] The aim of this small single center study is to compare the outcome of children older than one year with NBL treated at our center with other published studies.[9-11] Although the percentage of children with metastatic NBL in this study is comparable to other studies, any comparison is difficult as we relied on clinical prognostic factors only. Besides, many patients in our study were unwell and severely malnourished on arrival to our center. This in addition to other local factors and distance from the oncology service resulted in delay in starting treatment. Ten of 34 patients with stage 4 NBL were very unwell and emaciated at initial presentation and did not tolerate chemotherapy well. They eventually died because of disease progression or toxicity during induction chemotherapy. The remaining 24 patients received conventional treatment followed by complete or partial surgical resection and local radiotherapy was added in patients with residual tumor post surgery. The small number of patients makes it difficult to draw conclusions on the benefit of surgical resection in stage 4 patients. Relapse of the primary tumor was an important cause of treatment failure in stage 4 disease and was associated with a poor outcome. The only survivor among relapsed patients, was a 13-month-old child who relapsed at the site of primary tumor. The outcome of stage 4 patients is very disappointing and inferior to other published results. There is evidence that high-dose therapy (HDT) and autologous stem cell rescue can improve EFS in children with advanced NBL.[6,7] The delay in starting treatment and the lack of facilities to use HDT and

stem cell rescue might have contributed to our inferior results. The prognosis of children with stage 3 NBL varies according to age at diagnosis and histologic and biological features.[2,14] Infants enjoy a 4-year EFS of 93% compared to 54% for patients older than 2 years with unfavorable biologic features.[15] We are encouraged by the results of our study, but the lack of facilities to complete biological studies in our center meant that all patients were similarly treated. Future treatment may be modified according to the risk category as giving less intensive treatment to patients with favorable biological features will help to reduce long term morbidity.

Historically, many patients with stage 2 NBL received chemotherapy. Several single center and cooperative-group studies have shown no detrimental impact on survival from the elimination of chemotherapy, and approximately 20% of patients require therapy other than surgery.[15,16] The 5-year EFS in a Children's Cancer Group (CCG) study for children treated with surgery alone was 81% for stage 2B and 98% for stage 2A.[16] In the same study, 7/23 patients with incompletely resected disease developed recurrence, and all were successfully salvaged with further surgery or multimodality chemotherapy. Three out of 6 patients in our study were treated with primary surgical resection only, and the remaining 3 received chemotherapy followed by complete surgical resection. All survived in CR.

In conclusion, this small study confirms the good outcome of localized NBL in children more than one year. The use of high-dose and differentiating therapy may help to improve the results of patients advanced disease. Toxicity was significant, and the adoption of a risk-category for treatment may help to reduce treatment complications.

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