Neuroblastoma

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ABSTRACT

Objective: Due to the poor results achieved on combination chemotherapy and the unproven cost-effectiveness value of myeloablative therapy, the question has been raised; should patients with stage IV neuroblastoma be actively treated? The aim of the current study is to analyze retrospectively treatment results of 43 children with neuroblastoma with special stress on the rate and duration of remission in children with disseminated neuroblastoma.

Methods: Treatment of children with neuroblastoma consisted of surgical removal of the tumor, if possible, followed by chemotherapy for unresectable residual tumor including metastases. Second look surgery was performed to resect residual masses rendered resectable on chemotherapy in the absence of distal metastases. The chemotherapy protocol used in the current study consisted of alternating combination chemotherapy regimens containing, Cyclophosphamide, Vincristine and Doxorubicin, alternating with Cis-platinum and Etoposide.

Results: The male to female ratio was 2:1 with a median age of 2.1 years. The abdomen was the primary site of involvement encountered in 32 patients (74%). According to the childrens cancer study group (CCSG) staging system, only 6 patients (14%) had localized tumors (stages I and II). Two patients (5%) were found to have stage IV. Stage III was documented in 5 patients (12%). The majority of patients (70%) had disseminated disease at presentation. The bone marrow was the most common site of metastatic deposit, encountered in 23 patients out of the 30 with stage IV disease (77%). Out of the 12 evaluable non-stage IV patients, only one patient (8%) showed treatment failure. Assessment of response by the end of the 6th month from the date of diagnosis revealed that out of the 27 evaluable patients with stage IV, 4 patients achieved complete remission, 7 patients achieved very good partial remission, 8 patients achieved partial remission and 4 patients achieved mixed response. Three patients showed progressive disease on chemotherapy. Twenty-one patients (78%) were symptom-free and were conducting normal life. Assessment of response to treatment by the end of the 12th month from diagnosis revealed that 6 patients (2 complete remissions, 1 very good partial response, 3 partial responses) were maintaining their remission. Out of the 19 patients showing complete or partial remission at early assessment, 4 patients maintained their remission for more than 18 months. Two (one was in complete remission and the other was in partial response) of them progressed in areas of previous involvement after 20 and 21 months. The other 2 patients (one was in complete remission and the other was in partial response) showed disease progression in areas not previously affected by disease at presentation after 23 and 42 months.

Conclusion: Results of treatment by multiagent chemotherapy regimens used in the current study show that children with neuroblastoma, even those with advanced stages, should receive the benefit of intensive multimodal therapy, even those with partial response to initial therapy. These patients may experience reasonable symptom-free and sometimes, disease-free survival.

Keywords: Neuroblastoma, chemotherapy.

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The development of drug resistance remains the major obstacle to cure children with neuroblastoma. Intensified treatment protocols have raised the survival rate from 64% to 93% for localized staged neuroblastoma. However, the results obtained for disseminated neuroblastoma remained poor with survival rates of 0% in 1967–1981 and 17% in 1985-1990.[1] The poor response of patients

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with metastatic neuroblastoma to aggressive combination chemotherapy programs stimulated investigators to include autologous bone marrow transplantation (BMT) in the management of such patients. Event free survival 2 years after BMT was reported to be 6% to 64% among progression – free patients with advanced neuroblastoma. The spectrum of results may reflect patients selection.[2-4] A retrospective analysis by the Pediatric Oncology Group showed no significant benefit of changing, in remission, from conventional therapy to BMT.[5] Even after intensive myeloablative consolidation therapy, nearly 56% of patients will relapse by 36 months post transplantation.[6] However some subsets of patients appear to benefit from consolidation high-dose therapy.[7-8] Therefore, the role of megatherapy in advanced neuroblastoma, as regards cost-effectiveness remains to be defined. The majority of patients with neuroblastoma referred to our center have advanced stages. Due to the poor results achieved on combination chemotherapy and the unproven cost-effectiveness of myeloablative therapy, the question has been raised; should patients with stage IV neuroblastoma be actively treated? The aim of the current study is to analyze retrospectively treatment results of children with neuroblastoma referred to our center with special stress on the rate and duration of remission in children with disseminated neuroblastoma treated by combination chemotherapy.

Methods. Between January 1993 and June 1999, all children with the diagnosis of neuroblastoma referred to the Paediatric Oncology Unit, Oncology Center, King Abdulaziz Hospital, Jeddah, Kingdom of Saudi Arabia, were included in the current study. Pre-treatment assessment included complete physical examination, complete blood count, renal and hepatic function tests, level of urinary catecholamines, radiological investigation including MIBG (metaiodobenzyl guanidine scan), bone scans and evaluation of lesions by ultrasonography or computerized tomography scans or both as required. Based on these clinical, laboratory and radiologic findings the patients were staged according to the CCSG classification system (Table 1). Treatment of children with neuroblastoma consisted of surgical removal of the tumor, if possible, followed by chemotherapy for unresectable residual tumor including metastases. The chemotherapy protocol used in the current study consisted of alternating combination chemotherapy regimens according to the following system: Cyclophosphamide 900 mg/m^2 I.V. D1; Vincristine 1.5 mg/m^2 I.V. D1; Doxorubicin 45 mg/m^2 I.V. D1; alternating with Cis-platinum 90 mg/m^{2}I.V. D1; Etoposide 100 mg/m^2 I.V. D2, D3, D4. Patients with stage IV were treated with combination chemotherapy including cyclophosphamide 150 mg/m^2 P.O. (Per Oral) D1 to D7 and doxorubicin 35mg/m^2 I.V. D8. Combination chemotherapy was repeated every 21 days. As soon as progressive disease was detected, treatment was discontinued. Three weeks after the 4th cycle, patients were reassessed clinically and radiologically. Surgical resection was attempted for tumor masses rendered resectable on chemotherapy in the absence of distant metastases. Radiation therapy was given to the tumor bed (up to 45 Gy) to treat possible micro or macro-scopic residual disease. Response to treatment was assessed by the end of the 6th and 12th month from diagnosis based on clinical, laboratory and radiologic findings. Treatment response for patients with stage IV was classified according to the Modified International Neuroblastoma Response Criteria (Table 2).[9]

Results. ***Patients characteristics.*** Forty-three children were referred to our center for further management between January 1993 and June 1999. The male to female ratio was 2:1 with a median age of 2.1 years. Five patients (12%) were younger than one year. Twenty-nine patients (67%) had an age ranging between 1 and 5 years. Nine patients (21%) were older than 5 years. The abdomen was the primary site of involvement encountered in 32 patients (74%). The thorax and paraspiral areas were the sites of primary tumor in 8 patients (19%). In 3 patients (7%), the disease was widely disseminated so that the site of the primary involvement could not be specified (Table 3). According to the CCSG staging system, only 6 patients (14%) had localized tumors (stages I and II). Two patients (5%) were found to have stage IV. Stage III was documented in 5 patients

Table 1 - Staging system for neuroblastoma (Children's Cancer Study Group, CCSG).

Stages	Classification
Stage I	Tumor confined to the organ or structure of origin
Stage II	Tumor extending in continuity beyond the organ or structure of origin, but not crossing the midline. Regional lymph nodes on the ipsilateral side may be involved.
Stage III	Tumor extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally
Stage IV	Remote disease involving the skeleton, bone marrow, soft tissue and distant lymph node groups.
Stage IV-S	As defined in Stage I or II, except for the presence of remote disease confined to the liver, skin, or marrow (without bone metastases).

Table 2 - Modified International Neuroblastoma Response Criteria. Definitions of response to treatment.[9]

Response	Primary Tumor	Metastatic Sites
Complete Response	No tumor	No tumor; catecholamines normal.
Very good Partial Response	Decreased by 90-99%	No tumor; catecholamines normal; residual ^{99}Tc bone changes allowed.
Partial Response	Decreased by > 50%	All measurable sites decreased by > 50%. Bones and bone marrow; number of positive bone sites decreased by > 50%; no more than one positive bone marrow site allowed.
Mixed Response	No new lesions; > 50% reduction of any measurable lesion (primary or metastases) with < 50% reduction in any other; < 25% increase in any existing lesion.	
No response	No new lesions; < 50% reduction but < 25% increase in any exisiting lesion	
Progressive disease	Any new lesion; increase of any measurable lesion by > 25% previous negative marrow positive for tumor	
^{99}Tc=technician (Isotope substance)		

(12%). The majority of patients (70%) had disseminated disease at presentation (30 patients with stage IV). The bone marrow was the most common site of metastatic deposit, encountered in 23 patients (77%) out of the 30 with stage IV disease (Table 3).

Treatment results by stage. 1. Patients with stages I and II: The six patients with resectable early staged disease were subjected to complete excision of the tumor. Post-operative assessment of 4 patients, 2 of them showed no evidence of residual disease and they were kept under follow-up. They were disease free for a mean period of 37.8 months (range 15-83 months). The other 2 patients showed increased uptake of MIBG over the site of the primary tumor [the abdomen (1) and the thorax (1) inspite of the absence of any macroscopic tumor on computerized tomography scan. Both patients received 6 cycles of the alternating chemotherapy regimens used in the current study. The patient with paraspinal thoracic primary tumor received, localized field irradiation after the end of the 6th cycle to treat possible residual microscopic disease. These 2 patients are maintaining complete remission for 15 and 22 months.

Patients with stage III. One patient was not evaluable for treatment results. Three out of the 4 evaluable patients were older than 1 year and had abdominal primary tumor. The 4th patient was 10 months old at diagnosis and he has paraspinal disease. Tumor specimens for histopathologic examination were obtained through exploratory laparotomy and partial resection of the abdominal disease (2 patients) and through computerized tomography guided biopsy (2 patients, one with abdominal and the other one with paraspinal disease). All the 4 patients received the alternating chemotherapy regimens used in the current study. One patient with abdominal disease showed tumor progression on chemotherapy. The other 2 showed good tumor response and were subjected to 2nd look surgery to excise residual tumor tissues. Both received post operative irradiation and chemotherapy was continued for a total of 9 cycles. They are in remission for 43 and 29 months from the date of diagnosis. The patient who presented with stage III paraspinal disease showed stable disease on chemotherapy. The possibility of tumor maturation was raised. He was subjected to 2nd look surgery and subtotal excision of the primary tumor that proved to be ganglioneuroblastoma. He is still under treatment.

Patients with stage IVs. The 2 patients with stage IV were 9 and 10 month old at diagnosis and had skin involvement in addition to the primary tumor (pelvis and abdomen). They received 6 cycles of combination chemotherapy. Both of them are maintaining the complete remission for 43 and 33 months from diagnosis.

Patients with stage IV. Three patients were not evaluable as regards treatment results. Out of the 27 evaluable patients, bone marrow aspirate showing

Table 3 - Clinical characteristics of 43 children with neuroblastoma.

Characteristics	No	%
Sex		
Male	29	(67)
Female	14	(33)
Site of metastataic deposit		
Bone marrow	23	(53.5)
Bones	15	(35)
Orbit and eyes	12	(28)
Distant lymph nodes	4	(9)
Liver	3	(7)
Lung	2	(5)
Skin	3	(7)

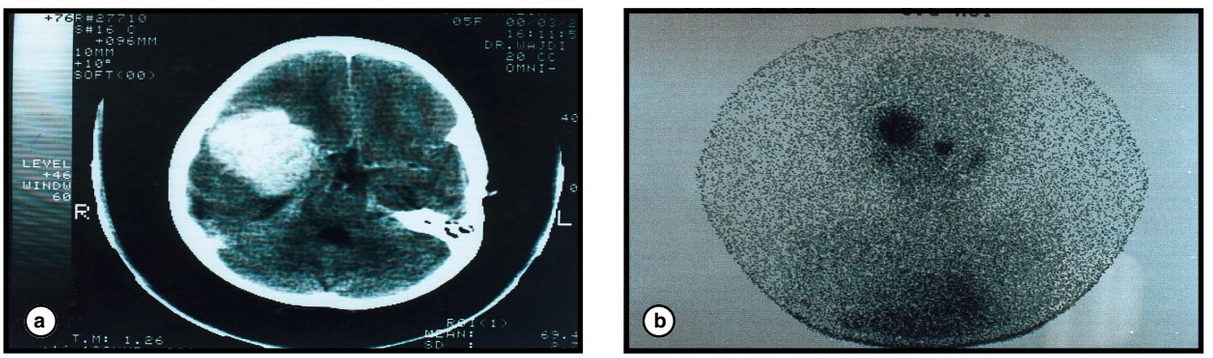

Figure 1 - **(a)** Computerized tomography brain scan showing dense soft tissue enhancing lesion in the right parietofrontal causing mass effect with mid-line shift. **(b)** Metaiodobenzyl guanidine (MIBG) scan showing intracaranial focal area of intense tracer accumulation at the right frontal area.

tumor cells in conjunction with typical clinical features confirmed the diagnosis of neuroblastoma in 17 patients (63%). Tumor specimens for histopathologic examination were obtained through surgical exploration (performed for biopsy or resection) in 10 cases (37%). Second look surgery was performed in 9 patients, where complete excision was possible in 3 patients. Four patients received post-operative irradiation to the tumor bed to treat possible microscopic (1) or macroscopic (3) residual disease. Assessment of response by the end of the 6th month from the date of diagnosis revealed that 4 (15%) patients achieved complete remission (CR), 7 (27%) patients achieved very good partial remission (VGPR), 8 (31%) patients achieved partial remission (PR) and 4 (15%) patients achieved mixed response (MR). Three patients (12%) showed progressive disease on chemotherapy. Twenty-one patients (78%) were symptom-free and were conducting normal life. Combination chemotherapy was to be continued for 12 months for all patients showing response. All patients tolerated the alternating regimen used in the current study well with no recorded serious morbidity. Only one patient died during induction therapy due to an infection-related complication. Assessment of response to treatment by the end of the 12th month revealed that 6 patients (2 CR, 1 VGPR, 3PR) were maintaining their remission, with 2 patients showing a mixed response and 18 patients showing no response or progression of the disease. One of the 27 evaluable patients with stage IV died during induction therapy. Out of the 19 patients showing complete or partial remission at early assessment, 4 patients maintained their remission for more than 18 months. Two (one was in CR and the other was in PR) of them progressed in areas of previous involvement after 20 and 21 months. The other 2 patients showed disease progression in areas not previously affected by disease at diagnosis. One of them was a girl of 5 years at presentation. She had primary abdominal disease with distant metastases to bones and bone marrow. In spite of being in complete remission documented clinically and radiologically for 23 months, she developed a solitary brain deposit on computerized tomography brain scan (Figure 1a) that was positive on MIBG scan (Figure 1b). She deteriorated rapidly while she was on whole brain irradiation. The 2nd patient was a girl of 4 years at presentation. She had primary abdominal disease with positive bone marrow and involvement of the orbit and eyes. She achieved partial remission on chemotherapy. She was subjected to 2nd look surgery. Partial excision of the tumor was performed followed by post-operative irradiation. Clinical and radiological assessment showed that she had persistent macroscopic abdominal disease, otherwise, there were no detected distant metastases. In spite of having residual disease in the abdomen, she maintained remission and was symptom-free for 42 months. Then, she started to complain of bony aches in the right femur that were not involved at presentation. Radiological investigation showed the picture of chronic bone process in the form of thickening of the cortex with sclerosis, periosteal reaction and soft tissue infiltration (Figure 2a) that was positive on MIBG scan (Figure 2b) and bone scan (Figure 2c). She received localized field irradiation to the site of metastatic deposit but refused chemotherapy. The patient showed no evidence of further disease progression for 10 months before she presented with disseminated disease.

Discussion. Neuroblastoma is an embryonal malignant tumor that usually affects children in the first 5 years of life. Approximately 50% of patients present with disseminated disease and with the exception of infants (age 0-11 months), have a poor prognosis.[10] In the current study, 65% of our patients had metastatic deposits at presentation. As reported

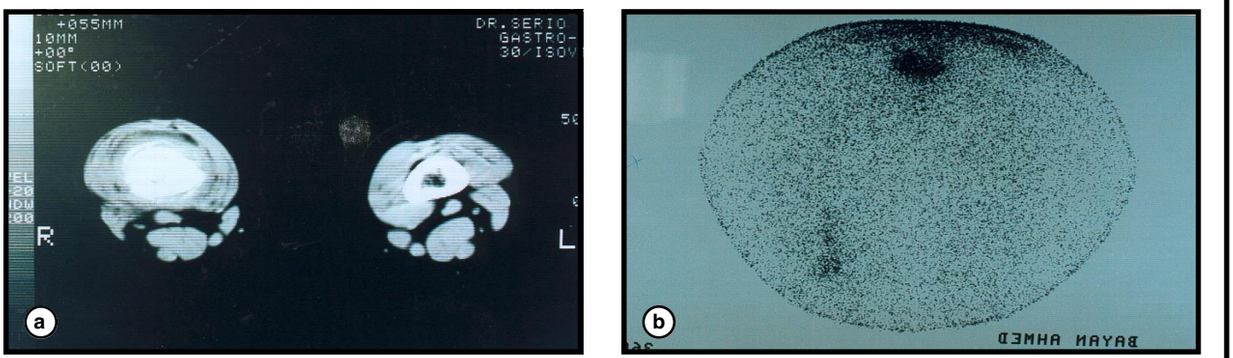

Figure 2 - (a) Computerized tomography scan of both femurs showing thickening of the cortex at the lower 1/2 of the right femur with sclerosis and periosteal reaction. There is soft tissue thickening surrounding the femoral shaft suggestive of a chronic process in bone with soft tissue involvement. **(b)** Metaiodobenzyl guanidine (MIBG) scan showing an increased tracer uptake is noted at the

in the literature,[11] the abdomen was the most common site of primary involvement and the bone marrow was the most frequently encountered site of metastataic disease among our patients. In cases without detectable metastases at diagnosis, surgical excision of the primary tumor radically, or with minimal local residual disease, may be sufficient therapy for most patients with low stage neuroblastoma, as residual disease does not usually grow or metasta and may spontaneously regress. Therefore, Matthay et al[12] and Kushen et al[13] suggested that non-stage IV patients without N-myc (MYCN) amplification can be spared cytotoxic therapy. In the current study, the response to treatment was excellent in patients with non-stage IV disease. However, some patients with stage III progressed on treatment. The availability of the biologic markers may help us in the future to identify the subset of patients who may need more aggressive therapy and those who may be cured by surgery alone without cytotoxic therapy. The highest risk population in neuroblastoma is older children with disseminated disease. With the suggestion that intensification of treatment may control disease more effectively, several multiagent treatment regimens have been developed.[14-21] In spite of improving initial response rates and perhaps prolonging time to progression of disease, the overall survival for this risk group (<15%) has remained essentially unchanged for the past decades.[11] In the current study, early assessment of tumor response showed that the majority of patients were achieving complete or partial remission and were symptom-free conducting normal life. Only 3 patients showed tumor progression while on chemotherapy. While, late assessment of response showed that 6 patients were maintaining their remission. Moreover, 4 of them maintained their remission for more than 18 months. It is interesting to notice that 2 of these 4 patients were in partial remission having residual tumor tissues. In spite of this, they maintained their response for 21 and 42 months without showing evidence of dissemination after discontinuing chemotherapy. The role that therapy played in these patients course is unclear. It is well known that intensive therapy can result in differentiation of an aggressive neuroblastoma but this differentiation is not generally associated with improved outcome.[22] However, Trebo et al[23] reported continued differentiation seen on sequential bone marrow samples after completion of therapy in a stage IV neuroblastoma patient suggesting that the maturation was due to the intrinsic tumor biology rather than

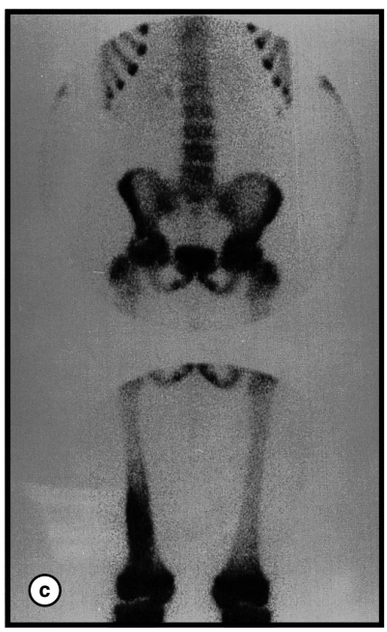

Figure 2 - (c) Bone scan showing mild increased tracer uptake at the distal part of the right femur.

the treatment. Sites of relapse for neuroblastoma tend to be multiple, but often occur in areas of previous disease. However, the intensification of chemotherapy that has prolonged survival in these children has changed the pattern of relapse presentation, as occurs with isolated central nervous system disease as the first or only site of recurrent disease.[24-26] These new relapse forms overshadow the prognosis of these children. In the patients showed tumor progression in sites previously involved with disease. One of them relapsed with isolated solitary brain deposit. A study that prospectively monitors children with advanced neuroblastoma radiographically and with CSF cytologies should help to define better the natural history of this type of metastases.

Neuroblastoma exhibits a diverse spectrum of clinical behaviour unparalled in human malignancy including tumors which regress spontaneously and those demonstrating chemo-resistance at presentation. For patients with advanced stage poor prognosis, the role of megatherapy remains to be defined. Although time to progression of disease is extended with this modality, questions yet to be resolved include the true impact on disease free survival in unselected patient cohorts. In addition to the high cost of megatherapy, still in the developing countries, the classic treatment of advanced neuroblastoma is by combination chemotherapy in conventional doses. However, stratification of patients into different therapeutic regimens based on biologic marks such as N-myc amplification may help to improve treatment results.[27] Results of treatment by multiagent chemotherapy regimens used in the current study show that children with neuroblastoma, even those with advanced stages, should receive the benefit of intensive multimodal therapy, even those with partial response to initial therapy. These patients may experience reasonable symptom-free, sometimes, disease-free survival.

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