Metastatic 4S neuroblastoma with excellent outcome in Saudi cancer center

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ABSTRACT

الأهداف: مراجعة بأثر رجعي لسلسلة صغيرة من ورم الخلايا البدائية العصبي (NBL) في مؤسسة طبية سعودية واحدة على مدى 10 سنوات، بما في ذلك تشخيصها وعلاجها ونتائجها.

المنهجية: اشتملت الدراسة على 53 طفل تتراوح أعمارهم بين 0 إلى 14 عامًا يعانون من ورم أرومي عصبي لم يتم علاجه سابقًا وتم تشخيصهم وعلاجهم في مركز الأميرة نورة للأورام، مدينة الملك عبد العزيز الطبية (KAMC)، جدة، المملكة العربية السعودية، خلال الفترة من 2010م و2019م. ستة أطفال (11.3%) لديها خصائص المرحلة 4S.

النتائج: كان متوسط العمر عند التشخيص 3 أشهر (من 52 يومًا إلى 4 أشهر). اظهرت الخزعات أن الغدة الكظرية كانت موقع الورم الرئيسي لثلاثة مرضى، بينما كان لدى الاثنين الآخرين مواقع خلف الصفاق. أربعة مرضى لديهم أنسجة ملائمة، ومريض واحد كانت لديه أنسجة غير ملائمة. كان لدى جميع المرضى ورم خبيث في الكبد، ولم يتم تسجيل أي نخاع عظمي أو ورم خبيث في الجلد. تلقى جميع المرضى العلاج الكيميائي باستثناء واحد، وجميعهم على قيد الحياة دون أي تقدم للمرض بمتوسط متابعة يصل إلى 5 سنوات.

الخلاصة: تؤكد بياناتنا أن NBL–4S هو سرطان قابل للشفاء، خاصة مع التشخيص والعلاج المبكر. العلاج الكيميائي هو خط العلاج الأول لمرضى الأعراض. لايستخدم العلاج الإشعاعي إلا إذا كانت الحالة مهددة للحياة. وتشير الدراسة إلى أن الاستئصال الجراحي عند الرضع الأصغر سنًا المصابين بأورام موضعية وبيولوجيا مواتية، وبخلاف ذلك، لا يُشار إليه عادةً للحالات المتبقية.

Objectives: To retrospectively review a small series of infant neuroblastoma (NBL) in a single Saudi medical institution over 10 years, including their presentation, management, and outcomes.

Methods: Fifty-three subjects aged 0 to 14 years with previously untreated NBL who were diagnosed and treated at Princess Nora Oncology Center, King Abdulaziz Medical City (KAMC), Jeddah, Saudi Arabia, between 2010 and 2019. Six infants (11.3%) had stage 4S characteristics.

Results: The median age at diagnosis was 3 months (range 52 days - 4 months). Biopsies confirmed that the adrenal gland was the primary tumor site for 3 patients, while the other 2 had retroperitoneal sites. Four patients had favorable histology, and one had unfavorable histology. All patients had liver metastasis, and no bone marrow or skin metastasis was recorded. All patients received chemotherapy except one, and all survived with no disease progression at a median follow up to 5 years.

Conclusion: Our data confirm that NBL-4S is a curable cancer, especially with early recognition and intervention. Chemotherapy is the first-line treatment for symptomatic patients. Unless the condition is life threatening, radiotherapy is not indicated. Surgical resection may be indicated in younger infants with localized tumors and favorable biology, but otherwise, it is not usually indicated for residual cases.

Keywords: neuroblastoma, International Neuroblastoma Staging System, 4S NBL (stage 4 special neuroblastoma)

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Neuroblastoma (NBL) is an embryonal tumor of the sympathetic nervous system that arises from the neural crest. It is the most common extracranial solid tumor during infancy and accounts for 7% of all childhood cancer diagnoses. Disease staging is an important prognostic factor and is used for risk stratification and treatment assignment. Stage 4s is defined as patients <12 months old with localized primary tumor, stage 1 or 2, and distant metastasis limited to the bone marrow, liver, or skin. It has excellent outcomes, and some patients develop spontaneous regression.

Large tumors may cause life-threatening compression of the lungs, kidneys, intestines, and inferior vena cava. In symptomatic cases, chemotherapy can be used for active regression and treatment. Asymptotic cases can be monitored by regular clinical, biochemical, and serial radiologic evaluations. We aimed to analyze the clinical presentation, age at onset, outcome of infants diagnosed to have stage 4(s) NBL and to compare with others.

Methods. The electronic data of 53 patients with NBL were retrospectively reviewed to identify cases of NBL (4S). The patients were selected from those who were diagnosed and treated at Princess Nora Oncology Center (PNOC), King Abdul-Aziz Medical City (KAMC), Jeddah, Saudi Arabia, from January 2010 to December 2019. The clinical characteristics and outcomes were examined. Ethical approval for the study was obtained from the ethic committee of KAMC.

The NBL patients were diagnosed based on the results of histopathology, immunohistochemistry, and molecular biology examinations (N-MYC, DNA ploidy, 1p and q 11 deletion, MKI) after surgical excision or open biopsy with reference to the onset age of <12 months. Staging was based on the International Neuroblastoma Risk Group Staging System (INRGSS) before surgery.[1]

Stage 4s disease was defined as local stage 1 or 2 with metastases isolated to the liver, skin, or bone marrow in an infant younger than 12 months of age. Tumor response was assessed using the International Neuroblastoma Response Criteria (INRC).[2] Patients were mainly treated with chemotherapy according to the children's oncology group (COG) ANBL1232 protocol, as shown in Table 1. None of the patients had surgery for residual disease (cases 4 and 6).

Result. Out of 53 retrospectively reviewed files, 6 patients (11%) were diagnosed with stage 4s NBL, and 4 patients were female. The median age at diagnosis was 3 months (range 52 days - 4 months). Biopsies confirmed that the adrenal gland was the primary tumor site for 3 patients, while the other 2 had retroperitoneal sites. For one patient, the diagnosis was made using clinical progressive hepatomegaly, respiratory distress, and radiological findings. Later, pathology results from the hepatic lesion revealed a poorly differentiated, non-amplified N-MYC pathology.

There were 4 patients with favorable histology and 2 with unfavorable histology. None of the N-MYC results were amplified. All patients had liver metastasis, and no bone marrow or skin metastasis was recorded. All patients survived with no disease progression at a median follow up to 5 years. The patients' characteristics and outcomes are shown in Table 2.

One patient did not require any medical or surgical intervention, while 5 patients received chemotherapy based on the clinical situation and Philadelphia clinical score for 4s NBL disease. The chemotherapy protocol used for the 5 patients was ANBL 1232, based on which 3 patients received 8 cycles, and 2 patients received 4 cycles, they showed complete clinical and radiological resolutions. The decision on the number of cycles was based on the patient's clinical condition and radiological response (mainly in computed tomography scans). All patients have survived, although 2 of them have a residual tumor that was <10% of the initial tumor mass size and required no secondary surgical intervention.

Discussion. Stage 4s NBL is a special infant tumor that represents 5% of NBL cases.[3] It has been established as having a significantly better prognosis than historical results with International Neuroblastoma Staging System stage 4 NBL in children. The P9641 and COG A3961 trials of the COG confirmed that excellent results are obtained for patients with low risk, including those with stage 4s and intermediate-risk disease. The 5-year event-free survival rate was 89%, and the over survival rate was 97%.[4,5] With only surgery, a younger infant (<6 months) with localized disease and favorable biology had an even better outcome.

In 2012, COG prospectively reported that 87 localized NBL cases involving patients <6 months old had a >90% 3-year survival rate after surgery only and observation.[6] This was recently confirmed by an Italian NBL group, which showed that patients who underwent early tumor resection were associated with better outcomes.[7] Even though the majority of patients present with metastasis, some of them have spontaneous regression, but 10-20% of infants do not survive due to early complications, which is mainly the result of massive hepatomegaly, renal obstruction, and coagulopathy.[8-10]

Table 1 - Chemotherapy schedules for symptomatic infant neuroblastoma (4S).

Cycles #	Chemotherapy Agents	Dosage	Day of treatment
1 and 7	Carboplatin	18.6 mg/kg/dose ≤ 12 kg or 560 mg/m²/dose > 12 kg	Day 1
	Etoposide	4 mg/kg/dose ≤ 12 kg or 120 mg/m2/dose > 12 kg	Days 1-3
2 and 6	Carboplatin	18.6 mg/kg/dose ≤ 12 kg or 560 mg/m²/dose > 12 kg	Day 1
	Cyclophosphamide	33.3 mg/kg/dose for patients ≤ 12 kg or 1000 mg/m2/dose for patients > 12 kg	Day 1
	Doxorubicin	1 mg/kg/dose for patients ≤ 12 kg or 30 mg/m2/dose for patients > 12 kg	Day 1
3 and 5	Cyclophosphamide	33.3 mg/kg/dose for patients ≤ 12 kg or 1000 mg/m2/dose for patients > 12 kg	Day 1
	Etoposide	4 mg/kg/dose ≤ 12 kg or 120 mg/m2/dose > 12 kg	Days 1-3
4	Carboplatin	18.6 mg/kg/dose ≤ 12 kg or 560 mg/m²/dose > 12 kg	Day 1
	Etoposide	4 mg/kg/dose ≤ 12 kg or 120 mg/m2/dose > 12 kg	Days 1-3
	Doxorubicin	1 mg/kg/dose for patients ≤ 12 kg or 30 mg/m2/dose for patients > 12 kg	Day 1
8	Cyclophosphamide	33.3 mg/kg/dose for patients ≤ 12 kg or 1000 mg/m2/dose for patients > 12 kg	Day 1
	Doxorubicin	1 mg/kg/dose for patients ≤ 12 kg or 30 mg/m2/dose for patients > 12 kg	Day 1

Table 2 - Patient's characteristics, treatment plan, and outcome.

Case	Age (days)/ gender	Primary site	Metastatic lesion	Histology	N-MYC	Clinical Philadelphia* Score		Chemotherapy # cycles	Follow up (month)	Outcome
						Initial prsentation	At progression			
1	52/M	Right supra-renal	Hepatic lesions	Poorly differentiated	NA	0	1	8	84	Alive
2	98/F	Bilateral supra-renal	Hepatic lesions	FH	NA	0	0	0	81	Alive
3	82/F	Retroperitoneal	Hepatic lesions†	Poorly differentiated	NA	0	1	4	45	Alive
4	104/F	Right supra-renal	Hepatic lesions	FH	NA	2	2	8	41	Alive
5	114/M	Retroperi-toneal	Hepatic lesions	FH	NA	0	1	8	33	Alive
6	65/F	Left supra-renal	Hepatic lesions	FH	NA	0	1	4	31	Alive

*Adapted from "Hepatomegaly in neuroblastoma stage 4S: criteria for treatment" by Hsu et al.[7] 0=asymptomatic, 1=mild/moderate, 2=severe, organ function compromise, F: female, M: male, NA: not amplified, FH: favorable histology (children younger than 18 months with a low or intermediate mitosis-karyorrhexis index; A differentiating or partially differentiating tumor and not amplified [N-MYC]). †Hepatic lesion biopsy after 1st cycle of chemotherapy.

There are no clear guidelines regarding the justification to start chemotherapy or the choice of combination regimens. We utilized chemotherapy as a first-line modality in 5 patients (cases 1, 3, 4, 5, and 6), which proved to be effective and was well tolerated. Clinical data suggest that the combination of carboplatin and etoposide is preferable as a first-line treatment, and a more intense chemotherapy or radiotherapy should be used for refractory cases.[11]

Only one infant who required no intervention and displayed a complete resolution of primary and metastatic tumors, while the other 2 (cases 4 and 6)

continue to have a residual tumor after 8 months since the initial diagnosis, but they remain asymptomatic. None of our patients required urgent radiotherapy or surgical intervention. In addition, none of them developed spontaneous abdominal compartment syndrome during or after biopsy. All patients survived with no disease progression at a median follow up of 5 years. Our results confirm those of a previous successful study carried out in the same institution by Najla et al.[12]

Study limitations. Our case series is limited by its retrospective nature and small size number of infants included. It would be a reference for further collaborative study of collecting more patients to draw more of conclusions and strengthen the studies.

In conclusion, stage 4s NBL is a distinct tumor that may undergo spontaneous regression. Chemotherapy is the first-line treatment for symptomatic patients. Unless the condition is life threatening, radiotherapy is not indicated. Surgical resection may be indicated for younger infants with localized tumor and favorable biology, but otherwise, it is not usually indicated for residual cases.

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