Neuroblastoma: Can lessons from the past help to improve the future?

L Coopoosamy, MMed (Paed); **J Schoeman**, MSc Dietetics; **D T Reynders**, FCPaed (SA), Cert Med Oncol (Paed) (SA); **F E Omar**, Cert Med Oncol (Paed) (SA); **A Büchner**, MMed, Cert Med Oncol (Paed) (SA), MPhil (Pall Med)

Department of Paediatrics and Child Health, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa

Corresponding author: *L Coopoosamy (lurisha.coopoosamy@up.ac.za)*

Background. The outcome of patients with neuroblastoma in South Africa has always been very poor. We conducted a retrospective study in one state-funded paediatric oncology unit (POU), to describe the clinical course, evaluate prognostic factors and report outcomes of patients with neuroblastoma.
Methods. We analysed routine data from one POU, gathered between 1993 and 2018. Kaplan-Meier curves were used to illustrate 2-year survival rates and to evaluate possible prognostic factors.
Results. Data from 87 patients were included and analysed. The median age was 41 months. The majority of the patients presented with stage 4 disease (77%). The most common presenting symptoms were bone pain, loss of weight, and abdominal distention. Chemotherapy was administered to 74 patients, and only 5 patients (6%) received palliative chemotherapy as first-line treatment. Only 18 of the 87 patients had surgery (21%) and 13 of 87 had radiation (15%), while 10 patients received palliative radioactive iodine (^{131}I-miBG) therapy. Patients with ferritin levels >120 ng/dL did not have a poorer outcome, and those with a raised lactate dehydrogenase (LDH) level displayed a shorter survival time but it was not statistically significant. The 2-year overall survival was 24% for the whole cohort and 16% for the stage 4 patients at diagnosis.
Conclusion. Neuroblastoma is a disease with a dismal outcome in our POU, mostly as a result of late presentation. To improve prognosis the focus should be on recognising danger signs to ensure early diagnosis and referral. We recommend adding danger signs for childhood cancer to the Integrated Management of Childhood Illness (IMCI) strategy in an attempt to improve early recognition and diagnosis of childhood cancer.

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Cancer can be defined as an abnormal growth of cells, which tend to proliferate in an uncontrolled way, and in some cases metastasise and spread.[1] More people die from cancer every year than from AIDS, tuberculosis and malaria combined.[2] According to GLOBOCAN 2018, the estimated number of new cases of cancer worldwide in 2018 was 18.1 million, with 9.6 million cancer-related deaths.[3] Cancer is the second leading cause of death in children, and it was estimated that 1 190 children would have died from cancer in 2021.[4]

Neuroblastoma (NB) is an embryonal neoplasm arising from the sympathetic nervous system and patients can present with many different and nonspecific signs and symptoms.[5,6] NB generally occurs in children <5 years of age, with the median age at diagnosis being 17 months. It is the most common solid tumour diagnosed in children in the first year of life.[6] The incidence of NB in South Africa (SA) has not reflected the same pattern described in high-income countries.[7-9] Patients with NB in SA usually present late with metastatic disease, implying a poor prognosis and outcome.[10] It is clear that the focus in SA should be on early diagnosis, with the aim of preventing progression to metastatic stage 4 disease.

The role of different biochemical and other prognostic factors in NB has been extensively studied. In 1987 Evans *et al.*[11] published an analysis of prognostic factors in a group of 124 children from the USA. This group included mostly Caucasian children (88%) under the age of 2 years and 41% had stage 4 disease. Their most important finding was that raised serum ferritin was associated with poorer 2-year overall survival (OS). More recently, studies from India[12] and Italy[13] described the use of different biochemical markers in predicting NB outcome. In both these studies raised serum lactate dehydrogenase (LDH) levels were independently associated with worse prognosis. Neuron-specific enolase (NSE) was only significant as a good prognostic factor in stage 4 patients if the levels were <200 ng/mL. The group from Italy also made the valid comment that LDH and catecholamines are routinely tested in most patients worldwide at diagnosis of NB, and that it is an easy, cost-effective way of stratifying patients.[13]

A study by Hesseling *et al.*[7] published in 1999 included all children from the Western Cape Province of SA diagnosed with NB between 1983 and 1997. The findings in this small southern African cohort (n=48) demonstrated that serum LDH has a good prognostic value, with a raised LDH associated with a worse prognosis. This cohort was too small to conclusively prove that a raised ferritin level is also a poor prognostic factor. In the latest large SA study, ferritin >120 ng/dL was significant for poor prognosis and can be used as a threshold value in the SA setting.[14]

Improving early diagnosis for children with cancer in SA is not a novel idea. For the past 20 years, various local and international publications have emphasised the importance of early diagnosis with the aim of improving overall outcomes of childhood cancer in SA.[8,9,14-16] The South African Children's Cancer Study Group (SACCSG) published a document with their priorities in 2007, and achieving early diagnosis was the first priority.[16] The SACCSG adopted the St Siluan warning signs of childhood cancer; their warning signs were presented in Amsterdam in 2000.[18] In 2001, Poyiadjis *et al.*[18] embarked on a campaign to educate the public

and primary healthcare workers on the St Siluan warning signs. This campaign was followed by assessment of the efficacy of these warning signs in promoting awareness of cancer. The study concluded that awareness and referral numbers improved, but unfortunately there was no improvement in earlier diagnoses and identifying localised disease.[15]

NB is a heterogenous disease and treatment strategies have evolved through the years according to the different biological features of these tumours.[6] As in all childhood malignancies, the greatest challenge is to use the treatment strategy with the best outcome and the lowest possible intensity, in order to limit side-effects and complications that could occur with treatment, especially treatment of higher intensity.[6]

The aim of this study was to describe the clinical course of NB in patients treated at the paediatric oncology unit (POU) of Kalafong Provincial Tertiary Hospital and Steve Biko Academic Hospital in Pretoria, with the main objective being to describe the value of possible prognostic factors in this group of patients.

Methods

A retrospective descriptive file review was conducted at a single POU originally situated at Kalafong Provincial Tertiary Hospital (1993 - 2009), and now at Steve Biko Academic Hospital (2010 - 2018) in Pretoria, Gauteng. The POU offers treatment to all patients from northern Gauteng and Mpumalanga provinces, as well as some patients from Limpopo Province and the neighbouring countries Zimbabwe and Mozambique.

All newly diagnosed patients with NB aged <18 years were considered for inclusion. A total of 100 patient files were reviewed; 13 files were excluded because of incomplete data, leaving 87 included in the study. The research protocol was approved by the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (ref. no. 493/2016) as well as the Faculty of Health Sciences MMed Committee of the University of Pretoria. Consent was obtained from the chief executive officer of Steve Biko Academic Hospital to access patient files and information. Data were anonymised using a unique study number to ensure confidentiality. There was minimal risk to patients because this was a retrospective audit of files with no direct involvement of patients.

The data were analysed in a quantitative manner and captured in an Excel datasheet (Microsoft Corp., USA) and transferred into Stata and SPSS version 20 (IBM, USA). Descriptive statistical analysis was done on all the data, using Stata 13 (StataCorp., USA). Owing to the overwhelming number of patients that died, statistically significant analyses could not be performed in order to assess the significance of prognostic factors using *p*-values. However, Kaplan Meier curves were created to illustrate 2-year OS curves for the various possible prognostic factors.

Results

This study was carried out at a single POU. Table 1 illustrates the demographics of the patients included in the study. There were 15 (17%) children under the age of 1 year, with 78% diagnosed before the age of 5 years. The mean age at diagnosis for all 87 patients was 41 months. Only 2% of patients presented with localised stage 1 disease, 77% with stage 4 disease and 3% with stage 4S disease (Table 1).

Children presented with a large number of nonspecific symptoms; however, the diagnosis was made easier by patients presenting with a cluster of symptoms suggestive of NB. The cluster of symptoms usually comprised bone pain, loss of weight, abdominal distention and abdominal mass.

Table 1. Sociodemographic and clinical characteristics of patients at diagnosis

	n (%)
Gender	
Male	46 (53)
Female	41 (47)
HIV status	
Negative	64 (74)
Positive	4 (5)
Unknown	19 (22)
TB	
Negative	20 (23)
Positive	4 (5)
Unknown	63 (72)
Age groups, months	
0 - 12	15 (17)
12 - 60	53 (61)
60 - 120	14 (16)
>120	5 (6)
International Neuroblastoma Staging System	
1	2 (2)
2	3 (4)
3	12 (14)
4	67 (77)
4S	3 (3)

Of the 87 patients included, 85% (*n*=74) received chemotherapy and the remaining 15% (*n*=13) did not receive any chemotherapy. The reason for not treating with chemotherapy was end-stage disease, where patients died before treatment could be started or were sent home for palliative care. Two patients absconded before any treatment could be given. Options for palliative treatment in advanced or relapsed disease in this setting include oral metronomic chemotherapy (cyclophosphamide), radioactive iodine (^{131}I-miBG therapy), and external beam radiotherapy for pain in symptomatic sites of disease recurrence. Fig. 1 outlines the different chemotherapy regimens used in this group of patients. A second regimen was used as extended induction in a few cases but mostly as palliative chemotherapy in relapsed patients. All patients who received a second or third regimen died.

Of the 87 patients enrolled in the study, 83% died and 13% are still alive (absconded patients not included). The main reason why this disease entity resulted in such a high mortality rate is that most patients presented with advanced stage 4 disease. The 2-year OS for the whole cohort was 24% (Fig. 2).

Age at diagnosis was not a significant prognostic factor (*p*=0.320). Children living with HIV had a worse outcome than HIV-negative children. Despite the small numbers this difference in 2-year OS was statistically significant with a *p*-value of 0.03 (Supplementary Fig. 1; https://www.samedical.org/file/2011). An elevated serum LDH was present in 65% (*n*=44) of the 68 patients whose LDH levels were tested at diagnosis. The patients with high LDL levels at diagnosis (classified as >750 U/L) had a shorter survival time compared with the patients with LDH <750 U/L (*p*=0.06) (Supplementary Fig. 2; https://www.samedical.org/file/2012). With regard to serum ferritin levels at diagnosis, the value of 120 ng/dL was used as the deciding value (as discussed above); an elevated serum ferritin was present in 77% (*n*=39) of the 51 patients whose ferritin levels were tested

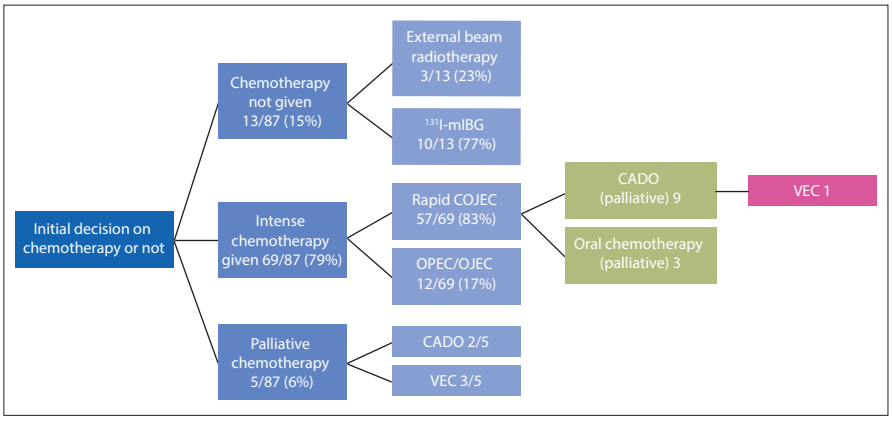

Fig. 1. Chemotherapy regimens used. (^{131}I-miBG = radioactive iodine; COJEC = cisplatin, vincristine (O), carboplatin(J), etoposide, cyclophosphamide; OPEC/OJEC = etoposide, vincristine and cyclophosphamide with alternating cisplatin (OPEC) or carboplatin (OJEC); CADO = cyclophosphamide, doxorubicin, and vincristine with continuous infusion cisplatin and etoposide; VEC = vincristine, etoposide, carboplatin.)

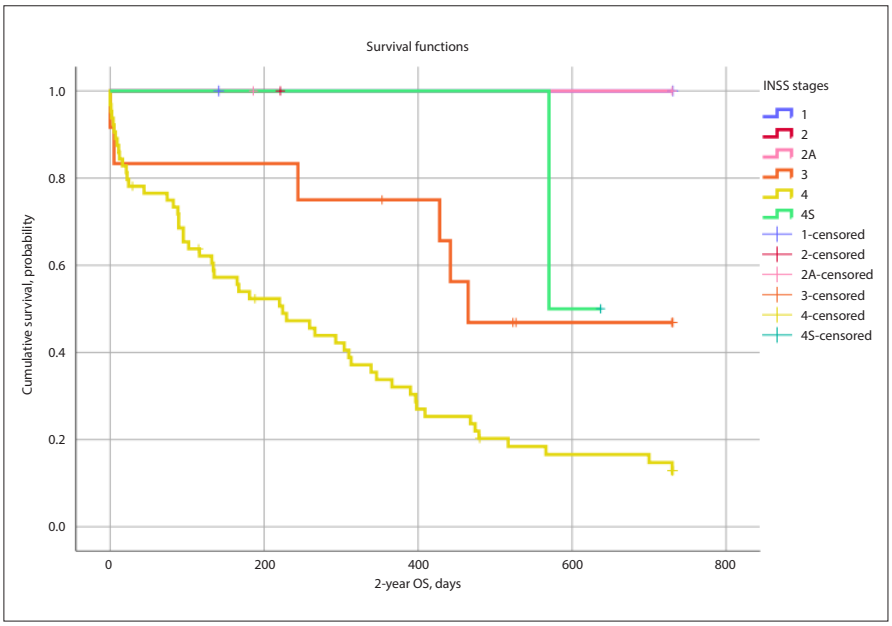

Fig. 2. Survival curve according to International Neuroblastoma Staging System (INSS). (OS = overall survival.)

at diagnosis (Supplementary Fig. 3; https://www.samedical.org/file/2013). Just as with LDH levels, the group of patients with elevated serum ferritin at diagnosis did not survive as long as the group with serum ferritin levels <120 ng/dL, but the difference was not statistically significant (p=0.079). *N-myc* testing, despite its historical importance in the staging of NB, was performed infrequently – only 10 patients had their histology sent for testing, of which 5 (50%) were positive. The patients with positive *N-myc* had a median survival of 17 months from diagnosis (range 6 - 18 months).

Discussion

This descriptive study of a cohort of patients with NB treated at the POU in Pretoria, SA, during the period 1993 to 2018 had the specific aim of describing possible poor prognostic factors associated with NB.

The male:female ratio of 1.12:1 in our study is similar to slight male predominance seen in most international and national groups.[18,19] Our small group of patients were significantly older at diagnosis, which is very similar to what was described in the larger SA study by Van Heerden *et al.*,[14] where the mean age was 39.9 months. International data from high-income countries describe a median age of 27 months at presentation,[20] compared with a mean age of 41 months in our group. In our study, 77% of patients presented with stage 4 disease, a much higher incidence than the 41.9% reported from the European studies [19] and the 51.4% from Turkey.[21] Our incidence of stage 4 disease was more comparable with what has been reported from Kenya[22] (92%) and SA's larger cohort (70%).[18]

The most common presenting symptoms in our group were bone pain, loss of weight and abdominal distention, followed by abdominal mass, fever, lower limb weakness and night sweats. These are general nonspecific symptoms that may be present as part of a number of disease entities besides NB. The combination of multiple symptoms in one patient should alert the attending physician to the possibility of NB. The St Siluan warning signs for childhood cancer include most of the common presenting symptoms found in our study group, except for abdominal distention and abdominal mass.[14] These warning signs are shown in Fig. 3, and should be used as a general guideline for patients and family members in rural SA to indicate that they need to seek medical attention immediately.

The values for serum ferritin and LDH described by the International Society of Pediatric Oncology-Pediatric Oncology in Developing Countries (SIOP-PODC) group to be predictive of outcome in NB are 120 ng/dL and 750 U/L, respectively.[23] Despite the small number of patients in this study, when the 2-year OS curves are examined, the trend agrees with what has been described by the PODC. Patients who had a high serum LDH, who formed the majority of patients in our study, had a shorter survival time than those with lower serum LDH. Ferritin values were increased in 76% of patients and those patients with values >120 ng/dL had shorter survival times. If patients present with symptoms suspicious of NB, serum LDH and ferritin levels should help facilitate earlier referral in patients where these values are markedly raised.

One of the limitations of this study was that the study population was relatively small. A larger sample size would perhaps represent the data more accurately. This was a single POU study carried out in two different settings. The relocation of the unit itself could have resulted in data being lost from files. The documentation of patients' information, tests performed, investigations carried out, treatment implemented, and other data were not standardised. This may lead to data not being accurately compared. During this study period access to genetic tests such as *N-myc* amplification and nuclear medicine procedures were limited, and this could possibly have impacted negatively on risk stratification determination, as well as staging of disease and overall outcome.

As was shown in the assessment of using the St Siluan warning signs in SA previously, a single campaign to optimise early diagnosis of cancers such as NB is not a long-term solution.[15] Owing to the

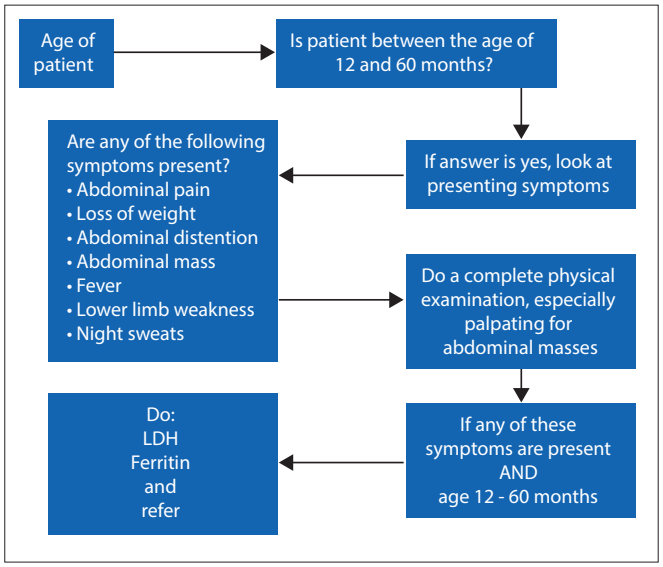

Fig. 3. Algorithm that could be included in the Integrated Management of Childhood Illness (IMCI) manual. (LDH = lactate dehydrogenase.)

fast turnover of healthcare providers in the country, these warning signs need to be continually taught as part of medical and nursing curricula. They should also be part of all information sessions held in primary care clinics, and primary care screening using systems such as the Integrated Management of Childhood Illness (IMCI) strategy.

Conclusion

NB is a disease with a dismal outcome in Pretoria, mostly as a result of patients presenting with stage 4 disease. Despite the initial good response of most patients (including those with advanced disease) to intensive chemotherapy and surgery, more than 50% of patients with high-risk NB can be expected to relapse and die. To improve prognosis the focus should be on recognising danger signs and referral for early diagnosis. Including danger signs of childhood cancer in the IMCI documents and guidelines should improve recognition and diagnosis at primary healthcare levels. Additionally, multicentre pooling of data should be conducted to develop and test an early diagnosis algorithm. Such an algorithm (see Fig. 3) could be included in the IMCI manual if it is feasible, practical, and easy to understand and implement at primary care level.

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