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Analysis of factors that may affect the therapeutic course of neuroblastoma. Summary of 17 years of own experience and literature review

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ABSTRACT

Introduction: Neuroblastoma (NB) is the fourth most commonly diagnosed childhood cancer. The stage of the disease at the time of diagnosis has an impact on treatment outcomes and survival. The aim of this study was to analyse factors that may affect the therapeutic course of NB.

Material and methods: The study group consisted of 77 patients. When analysing the time between the first visit to the doctor and the start of oncological treatment, significant differences were found between the group of patients with complete remission and the group that did not respond to treatment.

Results: Over the 17 years of the study, there was a tendency for the diagnosis of NB in the lower, 1st and 2nd stages of NB to increase. The stage of the disease correlated with the risk of disease progression, relapse, and risk of death. Although our study did not show a significant correlation between the timely implementation of the HR-NBL SIOPEN and the LINES protocols and the effectiveness of treatment, it proved that the period of time between the first visit to the doctor and the start of oncological treatment significantly affects the final response to the applied therapy.

Conclusions: The mild trend towards more frequent diagnosis of lower stage patients and prenatally detected cases may be related to increased availability of ultrasound and improved parental education.

KEY WORDS: prognosis, prognostic factors, child, neuroblastoma, cancer treatment protocol.

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INTRODUCTION

In children, and especially in newborns and infants, early detection of cancer often results from extreme alertness and forethought on the parents' part and, most importantly, from their knowledge of potential diseases [1-4].

Neuroblastoma (NB) is the most common extracranial solid tumour in children, accounting for 8% to 10% of all childhood cancers. It is the fourth most commonly diagnosed childhood tumour after acute leukaemias, lymphomas, and brain tumours. The annual incidence of NB ranges from 6 to 11 new cases per million children aged 0-15 years. In Poland, approximately 70-80 new cases are diagnosed each year [5]. NB develops from stem cells of the nervous system, usually originating from the sympathetic nervous system. Its typical location is the adrenal glands and the retroperitoneal space. It is the most common neoplasm in infancy. Up to 90% of NB cases occur before the age of 5 years [6].

Prognosis in NB depends on so-called prognostic factors, which include clinical, histological and biological-genetic factors. The International Neuroblastoma Staging System (INSS) classifies patients into groups 1 to 4 and 4s depending on the stage of the disease process and age. In subsequent years, a new classification system was proposed by the International Neuroblastoma Risk Group (INRGSS), introducing the following definitions: stage L1: localized disease-free of Imagining Defined Risk Factors (IDRFs), stage L2: a localized disease with

IDRFs, stage M: disseminated disease, stage Ms: disseminated disease of the "special" type (corresponds to 4s). Imaging risk factors according to the location of the tumour were described by Monclair *et al*. in 2015 [7].

The comprehensive treatment of NB depending on the risk group consists of chemotherapy, radiotherapy, surgical treatment, haematopoietic stem cell transplantation, immunotherapy and treatment of minimal residual disease. Individualisation of treatment and its intensity are associated not only with a better prognosis, but also with a reduction in the toxicity of the applied treatment and the risk of late complications related to anticancer treatment [8-10].

Neoplastic diseases in children are rare. Increased parental awareness of childhood malignancies and greater availability of ultrasound examinations, performed increasingly in asymptomatic infants and young children, may result in the diagnosis of NB at lower stages of the disease. We wanted to investigate whether such a trend occurs based on our material.

The aim of this study was to investigate known prognostic markers that may affect the course of the therapeutic process. We also analysed the incidence of NB in central-western Poland between 2004 and 2017, with particular emphasis on the stage of NB in each year of the study.

MATERIAL AND METHODS

The study group consisted of 77 children with NB, treated in the Department of Paediatric Oncology, Haematology and Transplantology, Poznań University of Medical Sciences, in the years 2004-2017. The observation of patients included in the study was completed on 30 January 2021. Patients were treated according to two protocols for "low- and intermediate-risk" and "high-risk" groups – these were the treatment regimens proposed in two European studies: LINES (Low and Intermediate Risk Neuroblastoma European Study) and HR-NBL SIOPEN.

The International Neuroblastoma Staging System (INSS) was used for the entire group of patients analysed. The distribution of NB stages across the years of the study was examined. Additionally, the course of treatment (depending on the risk group) and the occurrence of relapse or progression of the disease were carefully analysed. In addition, the timeliness and extent to which planned treatment was carried out within specific therapeutic protocols were examined. Particular attention was paid to the time from the first symptom of the disease to diagnosis and initiation of oncological treatment. The first symptoms of the disease included: lack of appetite, weight loss, fever, lethargy, pallor, weakness, irritability, anxiety, and symptoms caused by the presence of a tumour or metastases, such as abdominal enlargement, abdominal asymmetry, constipation, or diarrhoea, urinary disturbances, recurrent urinary tract infections, loss of motor function, walking difficulties, recurrent bronchopneumonia, enlarged lymph nodes, irregularity of the eyelid stroma (Horner's syndrome), blueberry muffin syndrome or opsoclonus-myoclonus syndrome.

MYCN gene amplification was investigated using the FISH technique with a probe for the *MYCN* gene and a control probe for the centromeric region of chromosome 2. *MYCN* gene copy number above 10 in relation to the signal number for the control probe indicated *MYCN* gene amplification.

Response to treatment was assessed using the following criteria: for complete response – no tumour, normal catecholamine secretion, for no response – no new lesion(s), reduction of lesion(s) < 50% with < 25% increase in any lesion(s) and for progressive disease – appearance of a new lesion; increase > 25% of any lesion; appearance of previously undetected marrow involvement. Relapse is the appearance of any NB foci after a complete response.

Statistical analysis was performed using Statistica software from StatSoft. Quantitative data were described by presenting the arithmetic mean and median. The Mann-Whitney *U* test and Student's *t*-test were used for significance and correlation analysis. Analysis of the effect of predictive factors on survival of children with NB was performed using logistic regression. Significance was set at < 0.05 in all tests performed.

The study was approved by the Bioethics Committee of Poznan University of Medical Sciences (Resolution No. 72/16, 14 January 2016).

RESULTS

In the analysed group of 77 children, 66 patients (85.71%) were alive. Eleven children died due to NB progression. Complete remission of the disease was achieved in 35 of the 66 children (53.03%), while a very good partial response to treatment was achieved in the next 31 patients (46.97%). Out of the 35 children who developed the disease before the age of 12 months, two of them died (5.71%), while in the group of 46 patients younger than 18 months, three of them died (6.52%). The highest number of deaths was observed in a group of 31 children diagnosed with NB at ≥ 18 months of age (8/31 – 25.81%).

The risk of death was significantly higher in the group of children whose treatment included chemotherapy, which was solely due to disease progression (p = 0.015). Deaths were observed only in the group treated according to the HR-NBL SIOPEN protocol, in the case of 11/49 children.

The primary tumour was most commonly located in the adrenal gland (53 children; 68.83%). Extra-adrenal localization in the abdominal cavity was found in 11 cases (14.29%) and in the mediastinum in 9 (11.69%) children. Distant metastases at the time of NB diagnosis were found in 37 patients (48.06%). There was a statis-

TABLE 1. Characteristics of the group of patients treated for neuroblastoma.

Parameter	*n*	%
Sex		
Boys	40	51.95
Girls	37	48.05
Age		
Range (months)	0-132	–
Median (months)	11	–
Number of patients < 12 months	35	45.45
Number of patients ≥ 12 and < 18 months	11	14.29
Number of patients ≥ 18 months	31	40.26
Time from symptom onset to doctor visit		
Detected prenatally or in the neonatal period		
< 1 month	16	20.78
	28	36.36
≥ 1 month	25	32.47
No data available	8	10.39
Time from doctor visit to initiation of oncological treatment		
Range in weeks	0-116	–
Median time in weeks	1	–
Stage acc. to INSS		
1	22	28.57
2	4	5.19
3	10	12.99
4	37	48.06
4s	4	5.19
MYCN amplification		
Absent	48	62.34
Present	18	23.38
Not examined	11	14.28
Treatment protocol		
LINES	28	36.36
HR-NBL	49	63.64
Chemotherapy		
Implemented	55	71.43
Surgery only	22	28.57
Treatment result		
Complete remission	35	45.45
Very good partial remission	31	40.26
Death	11	14.29

tically significant correlation between the presence of metastases and lack of response to treatment ($p < 0.001$).

NB is a tumour that localises to specific anatomical spaces. It causes life-threatening symptoms during surgery, referred to as imaging disease risk factor – IDRF. The risk of death in the group of patients with IDRF was significantly higher compared to the group of patients without these symptoms ($p = 0.029$). There was also a significant correlation between NB stage and the presence of life-threatening symptoms (IDRFs) ($p = 0.0002$).

Amplification of the *MYCN* gene was detected in 18/66 patients (27.27%). The *MYCN* amplification was analysed in individual age subgroups at the time of NB diagnosis (in age < 12 and < 18 months, ≥ 12 and ≥ 18 months) and in subgroups divided according to the disease stage. There was a significant correlation ($p = 0.017$) between the presence of *MYCN* gene amplification and non-response to treatment and survival in children with stage 4 disease ($p = 0.012$).

In the group of children who did not survive, the mean time from symptom onset to reporting to the doctor was 2.17 months (median: 1 month, range 0 to 6 months), while in the group of children who achieved a complete response, the mean time was 4.24 months (median: 1 month, range 0 to 5 months). There were no significant differences between the two groups ($p = 0.803$; Mann-Whitney *U* test). When analysing the time between the first visit to the doctor and the start of oncological treatment, significant differences were found between the group of patients with a complete response compared with the group that did not respond to treatment ($p = 0.031$). In the group of patients with a complete response, the mean time from the first contact with the doctor to the start of treatment was 0.192 weeks. In the group of patients whose outcome was defined as no response to treatment, the mean time was 0.898 weeks.

Table 1 presents detailed characteristics of the research group.

In 16 children (20.78%), who were completely asymptomatic, the tumour was detected incidentally during prenatal examinations ($n = 4$) or in an ultrasound examination performed after birth ($n = 12$). In the case of prenatal diagnosis of an adrenal tumour or in ultrasound in the first few days after birth, three children were left for 3-4 weeks' observation. None of them had spontaneous tumour regression and these children had to be surgically treated.

In the remaining 61 children, the mean time from the onset of symptoms to seeking medical attention and to the start of oncological treatment was analysed. In the non-survivor group, the mean time from symptom onset to seeking medical attention was 2.17 months (median: 1 month, range 0 to 6 months), whereas, in the group of children who achieved complete remission, the mean time was 4.24 months (median: 1 month, range 0 to 5 months). There was no significant difference between the two groups ($p = 0.803$; Mann-Whitney *U* test). When analysing the time between the first visit to the doctor and the start of oncological treatment, a significant difference was found between the groups of patients with

TABLE 2. Summary table presenting the impact of analysed prognostic factors on the response to treatment or risk of death.

Analysed factors		Statistical significance (*p*)
Factor 1	Factor 2	
Disease stage (INSS)	Risk of death	Yes ($p = 0.002$)
Disease stage (INSS)	Response to treatment	Yes ($p = 0.007$)
Occurrence of metastases	Response to treatment	Yes ($p < 0.001$)
Disease stage (INSS)	Disease progression and recurrence	Yes ($p = 0.009$)
MYCN gene amplification	Response to treatment	Yes ($p = 0.017$)
Time from the appearance of symptoms to seeking medical attention	Response to treatment	No
Time interval between the symptoms onset and the initiation of anti-cancer treatment	Response to treatment	No
Time interval between the diagnosis and the treatment initiation	Response to treatment	Yes ($p = 0.031$)
Presence of IDRFs	Risk of death	Yes ($p = 0.029$)
Presence of IDRFs	Disease stage (INSSRG)	Yes ($p = 0.0002$)
Progression during treatment or recurrence after treatment termination	Risk of death	Yes ($p = 1.338x10–7$)
Recurrence after treatment termination	Response to treatment	Yes ($p < 0.009$)
Occurrence of progression	Risk of death	No
Timely implementation of the therapeutic protocols	Response to treatment	No

**Response to treatment: CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease*
INSS – International Neuroblastoma Staging System, IDRFs – imaging-defined risk factors

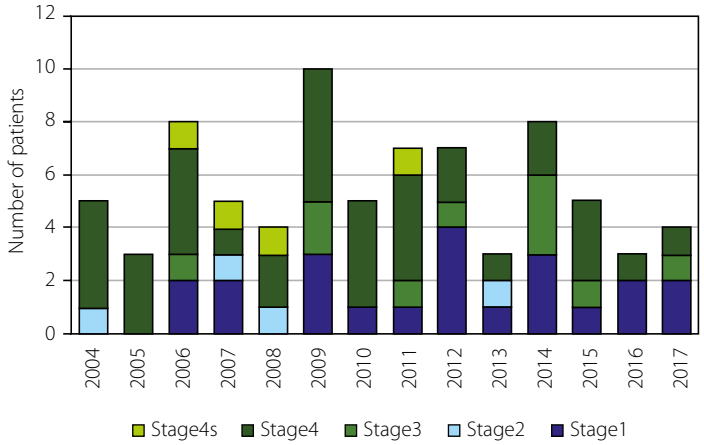

FIGURE 1. Distribution of the staging of neuroblastoma by INSS in each year of the study

complete remission and the group that did not respond to treatment ($p = 0.031$). In the group of patients with complete remission, the mean time from the first contact with the doctor to the start of treatment was 0.192 weeks. In the group of patients whose treatment outcome was defined as non-response to treatment, the mean time was 0.898 weeks.

Nearly 33% of patients were treated according to the LINES protocol, while about 64% of children were cured with HR-NBL SIOPEN. Chemotherapy was implemented in a total of 71% of patients, while only surgery was performed in 29% of children. In 26% of children the treatment additionally included radiotherapy. The analysis did not show a statistically significant correlation between the timely initiation of treatment and its effectiveness. There was also no significant difference between the group of patients with timely implementation of treatment and children in whom the treatment could not be carried out effectively (e.g. breaks in treatment, missed doses of drugs).

Progression during treatment or relapse after treatment was observed in 19 patients (24.68%). These occurred significantly more often in the group of patients whose disease ended in death ($p = 1.338 \times 10^{-7}$).

There was also a significant correlation between disease stage and the risk of disease progression and recurrence ($p = 0.009$). A significant correlation was found between relapse and non-response to treatment ($p < 0.009$). Progression despite the implementation of comprehensive treatment is a negative prognostic factor. However, there was no statistically significant correlation between the occurrence of progression and treatment outcome in the study group ($p = 0.194$). Overall, treatment was not completed due to progression or death in 13 patients (16.88%). In 11 children originally classified as low or intermediate risk, the treatment protocol was changed from LINES to HR-NBL SIOPEN. The reason for the change in treatment procedure was the occurrence of disease progression or relapse (in 7 and 4 children, respectively).

Table 2 summarizes the impact of analysed prognostic factors on the outcome of treatment.

The distribution of individual NB stages in each year of the study is presented in Figure 1. Over the 14 years of the examination, there is a gentle trend towards an increase in the diagnosis of NB at lower stages of NB.

DISCUSSION

NB accounts for 10% of all cancer cases and 15% of deaths in children with cancer [11, 12]. The stage of the disease at diagnosis affects treatment outcomes, survival, and prognosis. In stage 1, complete remission is possible in virtually 100% of children. In stage 2, the cure rate is 75%, in stage 3 it is 43% and in stage 4 it is 15% [13, 14]. According to the American Cancer Society, the five-year survival in children with NB depending on the risk group is as follows: 95%, 90-95%, and 40-50% for low, intermediate and, high risk groups for NB recurrence, respectively [15]. Our study showed that the stage of the disease had a significant impact on the risk of death in children. Death did not occur in the group of children classified by us as stage 1, 2, and 3 according to INSS, while it was present in 27% of children with stage 4. Moreover, it was found that children classified in the first three stages of the disease completed treatment as totally cured much faster. There was also a significant correlation between the stage of the disease and the risk of progression and relapse. Similar results and conclusions were obtained by other authors who described a high risk of relapse and treatment failure depending on the stage of the disease [16-18]. Iehara *et al*. reported that treatment failure was significantly more common in children with metastasis and IDRFs [19].

The time from the onset of distressing symptoms that prompted the parents to seek medical attention and to initiate treatment was analysed. The implementation of treatment was also evaluated in terms of timeliness, as well as deviations from the therapeutic protocol. The mean time from the onset of symptoms of the disease to the visit to the doctor was slightly longer than 2 months in the group of children in whom NB treatment failed and about 4 months in the group of cured patients. However, these differences were not significant. The long period of time between the onset of symptoms and the visit to the doctor may be due to the low socioeconomic status of parents and their poor knowledge of cancer in children. In the United States, a study was conducted to investigate the impact of Mexican emigration on the incidence and survival of patients diagnosed with cancer. Pinheiro et al. in their analysis detected a higher incidence of NB in children of Mexican natives compared to the rest of the population living in the United States [20]. In this case, it could be caused by the fact that migration is associated with economic instability and delayed health-seeking behaviour. Bansal et al. in their analysis of the Indian population showed that low social status and difficult access to professional medical help, as well as low knowledge and additional factors such as malnutrition and difficult access to certain medical procedures, have a significant impact on the survival of children with NB [21]. Parental education and access to health care, including ultrasound examinations, may therefore be important factors affecting the diagnosis, course of treatment and survival of children with cancer [22].

In NB, the presence of MYCN amplification is an important negative prognostic factor [23]. In the study group, MYCN gene amplification was detected in only 17% of infants, but already in 28% of children older than 12 months and in as many as in 26% of children older than 18 months at the time of NB diagnosis. Amplification of the MYCN gene was detected in only 4% of children at stage 1, but in a significantly higher proportion at more advanced stages of the disease – in 37% of children at stage 3 and in 32% of children at stage 4. Statistical analysis performed on the whole group of patients did not show a significant influence of the presence of MYCN gene amplification on survival. However, an effect of MYCN gene amplification on survival was found in the group of patients at stage 4.

An analysis of the frequency of NB stages in relation to the age of the patients showed an extremely uneven distribution. Stage 1 was found in 54% of infants, but only in 7% of children older than 12 months and in 3% of children older than 18 months. In contrast, stage 4 was detected in only 20% of infants, but in as many as 71% of children older than 12 months and in 77% of children older than 18 months. The course of treatment and the occurrence of progression/relapse or death were analysed in the study. Progression during treatment or relapse after the end of treatment was observed in almost 25% of patients. They occurred significantly more often in the group of patients in whom the disease ended with death. There was also a significant correlation between NB stage and the risk of progression and relapse. In the whole analysed group, 14% of children died. The highest number of deaths due to progression or relapse (nearly

26%) was observed in the group of children aged ≥ 18 months. In the group of children younger than 18 months at the time of NB diagnosis less than 7% of patients died. These data are known and available in several studies [24-27].

This study summarized our 17-year experience with NB treatment. Our examination did not show a significant correlation between the timely implementation of the HR-NBL SIOPEN and the LINES protocols and the effectiveness of treatment. However, our study showed that the period of time between the first visit to the doctor and the start of oncological treatment significantly affects the final response to the applied therapy (p = 0.031). The greater availability of ultrasound examinations and improved parental education may be associated with the earlier diagnosis of childhood cancer. A similar approach is highlighted in several studies in adults [28-32]. In the paediatric group, these data are still presented only sparsely [33, 34].

However, it is important to note that the effect of therapy in children with cancer, including NB, is not only influenced by the intensification of chemotherapy or the addition of new therapies such as autologous haematopoietic stem cell transplantation or immunotherapy, but also by better supportive care, including infection prevention.

CONCLUSIONS

In our group of patients, the stage of NB significantly influenced the risk of death. Also, the stage of the disease significantly correlated with the risk of disease progression and relapse.

Although our study did not show a significant correlation between the timely implementation of the HR-NBL SIOPEN and the LINES protocols and the effectiveness of treatment, it proved that the time period between the first visit to the doctor and the start of oncological treatment significantly affects the final response to the applied therapy. The mild trend towards the more frequent diagnosis of lower stage patients and prenatally detected cases may be related to increased availability of ultrasound and improved parental education. Improved parental education and the addition of screening in the form of periodic abdominal ultrasound examinations in children could increase the detection of lower stage tumours, resulting in favourable treatment outcomes.

DISCLOSURE

The authors report no conflict of interest.

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AUTHORS' CONTRIBUTIONS

PSS, MK, DJL prepared the concept of the article. PSS, MK collected and interpreted data. PSS and DJL wrote the article. All authors took part in preparing the final version of the publication.