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*Katarzyna Drabko[1], Anna Raciborska[2], Katarzyna Bilska[2], Jan Styczyński[3], Marek Ussowicz[4], Marta Choma[1], Beata Wójcik[1], Agnieszka Zaucha-Prażmo[1], Ewa Gorczyńska[4], Szymon Skoczeń[5], Wojciech Woźniak[2], Jolanta Goździk[5], Jerzy Kowalczyk[1]

Causes of treatment failure in children with Ewing's sarcoma in Poland treated with EURO-EWING 99 program (1999-2006)

Analiza przyczyn niepowodzeń leczenia dzieci z mięsakiem Ewinga w Polsce w latach 1999-2006 według programu EURO-EWING 99

[1]Department of Pediatric Hematology, Oncology and Transplantology, Medical University, Lublin
Head of Department: prof. Jerzy Kowalczyk, MD, PhD
[2]Department of Pediatrics and Adolescent Oncological Surgery, Institute of Mother and Child, Warszawa
Head of Department: Magdalena Rychłowska-Pruszyńska, MD, PhD
[3]Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz
Head of Department: prof. Mariusz Wysocki, MD, PhD
[4]Department of Pediatric Bone Marrow Transplantation, Hematology and Oncology, Medical University, Wrocław
Head of Department: prof. Alicja Chybicka, MD, PhD
[5]Transplantation Centre, University Children's Hospital, Kraków
Head of Department: Jolanta Goździk, MD, PhD

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Słowa kluczowe
mięsak Ewinga, niepowodzenia leczenia, dzieci

Summary

Introduction. Results of treatment of Ewing's sarcoma in children and adolescents are unsatisfactory and multidisciplinary efforts are necessary to improve the outcome of this patients.

Aim. Retrospective analysis of treatment failure children and adolescence with Ewing's sarcoma treated in Polish oncology centers.

Material and methods. Study included 119 patients with Ewing's sarcoma treated in 1999-2006 according to the EURO-EWING 99 program in five pediatric oncology centers. High-risk patients (78) were identified as those, who had at least one of the following factors: the presence of distant metastases at diagnosis, lack of primary tumor resection or poor histologic response to preoperative chemotherapy.

Results. In the study group 54 patients died. Most of the treatment failures in children with Ewing's sarcoma was caused by the underlying disease: lack of remission or relapse of the disease was the cause of death as many as 50 children (92%). Treatment related death occurred in 4 patients (8%). In high-risk patients relapse was observed in 44/78 (56%) patients and in 11/41 (27%) patients in standard risk group. The progression of the disease was the reason of death in 11 patients who did not respond to first-line therapy and their further treatment was not carried according to EURO-EWING 99.

Conclusions. Almost all treatment failures were due to the underlying disease, in our opinion intensification of therapy in high-risk patients in first remission is justified, with careful monitoring of late effects of this treatment. Use megachemotherapy in some patients with risk factors did not increase the number of deaths due to toxicity and contributed to reducing the number of relapses in these patients. New methods including experimental chemotherapy are required for patients with Ewing's sarcoma, who not respond to induction treatment.

Address/adres:
*Katarzyna Drabko
Department of Pediatric Hematology, Oncology and Transplantology
Medical University
ul. Chodźki 2, 20-093 Lublin
tel. +48 (81) 718-55-19
k.drabko@umlub.pl

Streszczenie

Wstęp. Wyniki leczenia mięsaka Ewinga u dzieci i młodzieży są niezadowalające i konieczna jest współpraca wielodycyplinarna w celu poprawy losu tych pacjentów.

Cel pracy. Retrospektywna analiza niepowodzeń leczenia dzieci i młodzieży z mięsakiem Ewinga leczonych w polskich ośrodkach onkologii dziecięcej.

Materiał i metody. Analizą objęto grupę 119 pacjentów w wieku od 1,5 miesiąca do 19 lat z mięsakiem Ewinga, leczonych w latach 1999-2006 według programu EURO-EWING 99 w pięciu ośrodkach onkologii i hematologii dziecięcej oraz chirurgii onkologicznej.

Pacjentami wysokiego ryzyka określono tych 78 chorych, u których stwierdzono co najmniej jeden z następujących czynników: obecność odległych przerzutów przy rozpoznaniu choroby, brak możliwości resekcji ogniska pierwotnego lub zła odpowiedź histologiczna na chemioterapię przedoperacyjną.

Wyniki. W badanej grupie zmarło 54 chorych. Większość zgonów u dzieci z mięsakiem Ewinga (50/54, 92%) była spowodowana brakiem remisji lub nawrotem choroby. U 4 pacjentów przyczyny śmierci były związane z leczeniem (8%). W grupie chorych z obecnymi czynnikami ryzyka wznowę stwierdzono u 44/78 (56%) pacjentów i 11/41 (27%) chorych z grupy standardowego ryzyka. Z powodu progresji choroby zmarło też 11 chorych, którzy nie odpowiedzieli na terapię I linii i ich leczenie nie było dalej prowadzone według programu EURO-EWING 99.

Wnioski. Niemal wszystkie niepowodzenia leczenia były spowodowane chorobą, co w naszej opinii uzasadnia intensyfikację terapii u pacjentów wysokiego ryzyka w pierwszej remisji, ze starannym monitorowaniem późnych skutków tego leczenia. Wykorzystanie megachemioterapii u pacjentów z czynnikami ryzyka nie zwiększyło liczby zgonów z powodu toksyczności i przyczyniło się do zmniejszenia liczby nawrotów w tej grupie pacjentów. Nowe metody, w tym terapie eksperymentalne są niezbędne dla pacjentów z mięsakiem Ewinga, którzy nie reagują na leczenie indukcyjne.

INTRODUCTION

Ewing's sarcoma (ES) is the second most common malignancy of bone after osteosarcoma, and bone tumors are the eighth most common cancer in childhood after leukemia, CNS tumors, lymphomas, neuroblastoma, soft tissue sarcoma, embryonic tumors and kidney tumors. Incidence of ES is according to various sources from 1.6 to 2.9 new cases per 1 million children per year. More often boys than girls are affected 1.3-1.8 to 1 respectively. Most cases are diagnosed between 15-19 year age group (40%). Polish data from 1995-1999 indicate a higher incidence of bone tumors in children in our country (8.2% of all cancers in children) as compared to the European data (4.2%) (1-5).

ES is a systemic disease, as evidenced by the results of treatment in the years when they were available only local methods: surgery and radiotherapy. The majority (> 90%) described patients despite resection or irradiation of the primary foci died within a few to several months after diagnosis because of distant metastases (6-8).

Nowadays treatment of ES is complex, therapeutic programs are based on clinical trials, and consisted of a combination of preoperative chemotherapy, surgery and consolidation therapy, which is based on risk factors at the time of diagnosis and response to induction therapy. Group of European countries: United Kingdom, Germany, Austria, Netherlands, France, Switzerland and other countries affiliated to the EORTC-STBSG (European Organisation for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group) has prepared a program EURO-EWING 99, which was registered in 2001 and the planned closing date of this Protocol in 2017 (9).

The program EURO-EWING 99, which was also recommended by the Polish Pediatric Solid Tumours Group as standard of care of patients with ES, identified the following prognostic factors, which determines stratification treatment groups of patients:

- the presence of metastases at diagnosis ES,
- location of metastatic (lung or other locations),
- the possibility of surgical resection of the tumor,
- histological response to preoperative chemotherapy,
- the size of the tumor – in the cases without possibility of surgical resection.

Determination of risk factors in Poland also was based on the criteria of the EURO-EWING 99. In the Polish centers decision of consolidation therapy in patients with an unfavorable prognosis was taken by physicians and patients were not randomized for conventional consolidation consisting of cycles of standard chemotherapy (vincristin, actinomycin, and ifosfamide) or megachemotherapy (busulfan and melphalan).

AIM

The aim of this study was a retrospective analysis of treatment failures of children and adolescents with Ewing's sarcoma treated at Polish pediatric oncology centers.

MATERIAL AND METHODS

The analysis of failures of treatment was performed on a group of 119 patients with ES, including 71 boys, treated in five Polish pediatric centers of oncology and hematology: Department of Surgical Oncology Children and Youth, Institute of Mother and Child in Warsaw and departments of Pediatric Oncology and Hematology in Lublin, Wrocław, Bydgoszcz and Kraków. The median age of patients studied at diagnosis was 13 years and 2 months. The youngest patient at diagnosis was 1.5 months and the oldest 19 years and 9 months. The location of primary site of ES in the study group are shown in figure 1. In patients included to the analysis, the presence of following high-risk factors were determined:

- the presence of distant metastases at diagnosis,
- lack of surgical removal of a primary tumour,
- more than 10% viable tumor cells in the primary tumor after preoperative chemotherapy (poor histological response to preoperative chemotherapy).

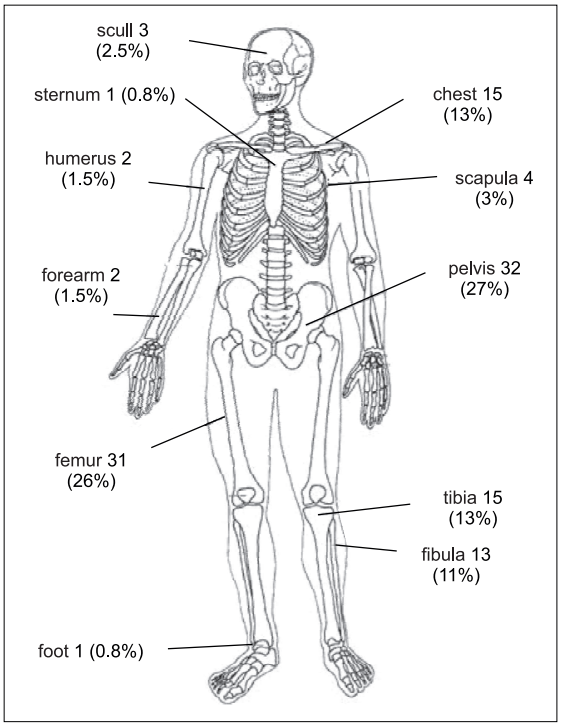

Fig. 1. Primary sites of Ewing's sarcoma in analyzed group.

Due to the nature of the retrospective analysis, not all patients had sufficient data to determine the volume of the primary tumor, and therefore in this study we not included the tumor volume as a risk factor. Standard risk patients (SR) were defined children who did not have any of these adverse factors. High-risk patients (HR) were determined the patients revealed the presence of at least one of the above mentioned factors of poor prognosis. In the analyzed group of patients 41 children was included to SR group and the other 78 patients were in HR group.

All patients received preoperative chemotherapy consisted of 6 cycles of 4 drugs: vincristine 1.5 mg/m^2, doxorubicin 60 mg/m^2, ifosfamid 9 g/m^2 and etoposide 450 mg/m^2, followed by surgery of primary tumor in all feasible cases (96 patients, 81%). Consolidation therapy was either 8 cycles of conventional chemotherapy (vincristine, ifosfamid and actinomycin D) or megachemotherapy consisted of busulfan 16 mg/kg and melphalan 140 mg/m^2.

Based on decision of treating physician, 35 HR patients received megachemotherapy and autologous hematopoietic cell transplantation (MCT and aHSCT) and 29 underwent conventional chemotherapy as a consolidation treatment in first remission. Seventeen children failed to achieve remission (11.9%) or progressed during preoperative chemotherapy or surgery (6.5%).

RESULTS

Median follow-up of the analyzed patients was 4.5 years (range from 5 months to 10.5 years). During observation time from the group of 119 patients with Ewing's sarcoma 54 patients died. Causes of death were as follows: in 39 (72%) children recurrence of the disease, 11 (20%) progressive disease after diagnosis without remission, 3 children (6%) treatment-related toxicity and 1 patient (2%) died of due to secondary tumor (fig. 2).

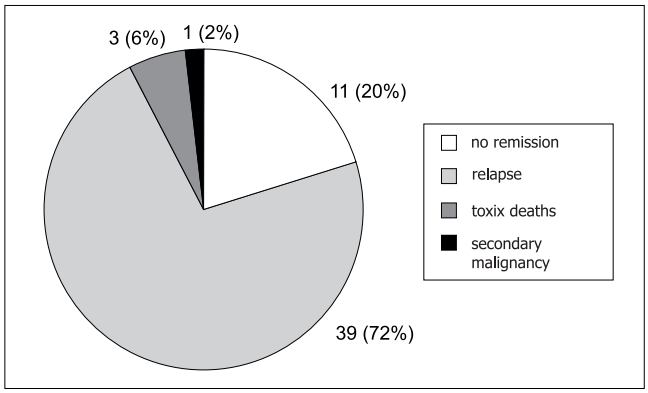

Fig. 2. Causes of death of patients with Ewing's sarcoma – EURO-EWING program.

Eleven patients who failed to get response to preoperative chemotherapy or progression occurred after surgery before the start of consolidation therapy, died due to disease progression in time from 9 to 36 months. Relapse of Ewing's sarcoma was diagnosed in 39 patients (38%) of the study group. From patients in the SR group recurrence of the disease occurred in 11 of 41 patients (27%) and in HR patients receiving busulfan and melphalan in the consolidation recurrence was observed in 9 of 35 patients (26%). Significantly higher relapse rate, 19 to 26 patients (73%), was observed in high-risk patients receiving conventional consolidation. The probability of recurrence was 40% in the whole group, as shown on figure 3.

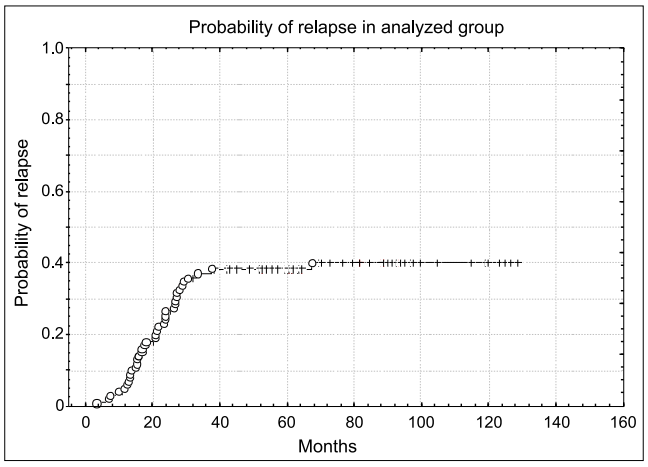

Fig. 3. Relapse rate in analyzed group.

Most of the treatment failures in children with Ewing's sarcoma was caused by the underlying disease: lack of remission or recurrence of the disease

was the cause of death 50 out of 54 children (92%). Treatment related causes of death were the cause of 4 patients (8%). After excluding these 11 patients and 6 patients who were treated with other chemotherapy regimens, relapse of Ewing's sarcoma occurred at different frequencies in risk groups SR and HR (fig. 4). Patients in the SR (n = 41) had 11 relapses of the disease, leading to the death and there were no other causes of treatment failure. In patients with HR group (n = 61) had a relapse that led to the death in a total of 28 children, including a 19/26 patients without megachemotherapy and 9/35 children who underwent treatment with busulfan and melphalan. A retrospective analysis of the efficacy megachemotherapy in patients with Ewing's sarcoma of the high-risk group showed, that its use significantly improves the prognosis in this group of patients, which is described in details elsewhere (10).

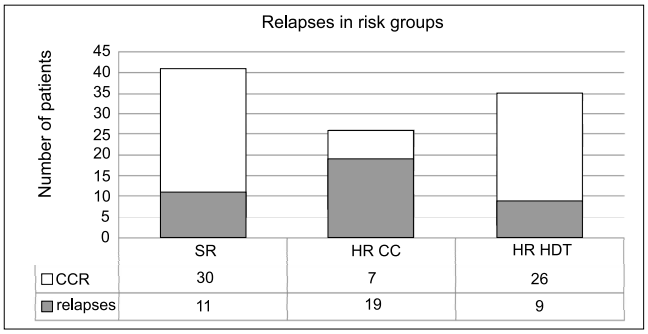

Fig. 4. Relapses in risk groups.
CCR – continued complete remission, SR – standard risk, HR – high-risk, CC – conventional consolidation, HDT – high dose chemotherapy

In four patients with HR features causes of death were related to treatment. The youngest patient, 1.5 months at the time of diagnosis boy, died of multiple organ failure at the age of seven months, after the fifth cycle of preoperative chemotherapy. In the second patient with the HR group, 15-year-old boy at the time of diagnosis, treated with conventional consolidation in 4.5 years after treatment, second cancer (osteosarcoma) was diagnosed and it was the cause of death of the patient.

Two children died after megachemotherapy 15-year-old girl died due to severe venoocclusive disease of the liver and multiorgan failure in the early period after megachemotherapy and 12-year-old boy died as a result of bleeding into the central nervous system 4.5 months after aHSCT.

DISCUSSION

In this study we collected information about the majority of children and adolescents diagnosed with Ewing's sarcoma, those treated in Polish pediatric oncology centers in the years 1999-2006. The cooperation between these centers makes both the same: oncological treatment and the conditions and standards of supportive care in all patients. It seems, therefore, that the conclusions drawn from the study are valuable, despite the retrospective nature of the analysis.

The Polish Pediatric Solid Tumor Group has so far failed to introduce routine analysis of translocation t(11, 22) or fusion gene EWS/FLI1 which, according to many authors are factors relevant to prognosis in this cancer (11). Recently published results of the analyzes do not confirm, however, clearly the importance of these genetic markers for the outcome of patients with ES and it seems that these relationships require further detailed studies (12, 13).

Still awaited is the publication of the results of the group conducting the study EURO-EWING 99, which was the first randomizing patients with risk factors between consolidation using conventional chemo- and megachemotherapy. Recently released the work summarizing the outcomes of this program in 281 patients with primary disseminated form of the disease, for which busulfan and melphalan as consolidation therapy was recommended. Due to the progression of the disease or the individual decisions of patients or physicians, the intensification of treatment was not administered to 112 patients. In 169 patients received MCT, of which at 136 with busulfan and melphalan. 3-year survival of patients with complete remission before MCT was 57% in patients with partial remission 32%, and in patients with stable disease 24%. Based on the findings of this large group of patients the authors developed a model predicting the course of disease in patients with primary metastatic ES. It was found that the factors of worse prognosis in these patients are: age over 14 years, metastases in the lungs, bones or bone marrow and tumor volume above 200 ml. For patients who are not in remission after standard induction treatment the authors recommend the use of experimental methods, enabling to control the disease (14).

Patients with recurrent or early progression of Ewing's sarcoma according to the most cited above authors are particularly unfavorable prognosis. Megachemotherapy, as a method of treatment, gives the best results as a consolidation of the first, or subsequent complete remission. Our own experience also shows that the use of busulfan and melphalan or total body irradiation (total body irradiation – TBI) in patients with disease progression, increases the risk of serious toxicity and does not improve the prognosis of those patients (15-17).

CONCLUSIONS

Results of treatment of Ewing's sarcoma in children and adolescents are unsatisfactory. Almost all treatment failures were due to the underlying disease, in our opinion intensification of therapy in high-risk patients in first remission is justified, with careful monitoring of late effects of this treatment. Use megachemotherapy in some patients with risk factors did not increase the number of deaths due to toxicity and contributed to reducing the number of relapses in these patients. New methods including experimental chemotherapy are required for patients with Ewing's sarcoma, who not respond to induction treatment.

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