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Acute complications of the treatment of Hodgkin's disease in children

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Introduction. Over 80% of children treated for Hodgkin's disease (HD) acquire long-lasting event free survival; however, oncological treatment is connected with multiple side effects.The aim of this study was to estimate the type and frequency of acute complications of chemo- and radiotherapy in children with HD.
Material and methods. 21 patients, aged 2.5 -17 years, treated for HD in the Department of Pediatrics, Hematology, Oncology and Endocrinology, Medical University of Gdańsk according to Protocol HD-95 or HD-97 were analyzed retrospectively. All of them achieved remission of neoplastic disease. We estimated incidence of hematological, infectious, gastric, hepatic, pulmonary and cardiac side effects.
Results. Severe myelosupression (IV° toxicity according to WHO scale) was the most frequent side effect observed in 17/21 patients (80.9%). Infectious complications, mainly opportunistic, were observed in 13 children. Gastrotoxicity of moderate intensity was observed in 6 children, predominantly after B-DOPA cycles. Hepatotoxicity was manifested as the increased aminotransferases serum levels. Only one patient with simultaneous hepatitis B infection demonstrated clinical symptoms of liver disorder with jaundice and hepatomegaly. Cardiac complications were revealed by echocardiographical examinations as a decreased ejection fraction of left ventricle (EF) in 6/21 children. Moreover one of them had pericardial effusion with adequate clinical signs of circulatory failure. Pulmonary toxicity was recorded in chest radiography of the youngest (2.5-yrs.) girl and was interpreted as pneumonia. The majority of all acute complications were transient and reversible, except for the fibrous changes in the lungs, which persisted.
Conclusions. Multimodal oncological therapy of HD may require hematopoietic growth factors to realize the protocol without delays brought on by severe neutropenia. The frequency of opportunistic infections calls for particular attention to proper epidemiological conditions throughout therapy. It is indicated to monitor several organ functions because of various complications, which may appear during and soon after the end of therapy.

Ostre powikłania leczenia choroby Hodgkina u dzieci

Wprowadzenie. W leczeniu choroby Hodgkina (HD) u dzieci osiąga się obecnie ponad 80% długoletnich przeżyć wolnych od zdarzeń, lecz stosowana terapia stwarza pewne problemy, związane z występowaniem powikłań dotyczących różnych narządów.
Celem pracy było określenie rodzaju i częstości występowania ostrych powikłań w czasie leczenia tej choroby u dzieci. Materiał stanowili pacjenci leczeni z powodu HD w Klinice Pediatrii, Hematologii, Onkologii i Endokrynologii AM w Gdańsku, zgodnie z programem HD-97, w latach 1994-1997. Wszyscy chorzy (21 pacjentów) osiągnęli remisję choroby. Analizie poddano uboczne objawy hematologiczne, infekcyjne, gastrotoksyczne, pulmotoksyczne i kardiotoksyczne, które wystąpiły w czasie prowadzonej chemio- i radioterapii.
Wyniki. Najczęściej (u 17 chorych) obserwowano objawy mielosupresji o znacznym nasileniu (IV° toksyczności wg WHO). Powikłania infekcyjne, głównie infekcje oportunistyczne, wystąpiły u 13 pacjentów. Objawy gastrotoksyczne o miernym nasileniu pojawiły się u 6 dzieci po cyklach B-DOPA. Hepatotoksyczność, manifestująca się wzrostem poziomu aminotransferaz, stwierdzono u 6 badanych, a u 1 z nich stwierdzono kliniczne objawy z pojawieniem się żółtaczki. Był to chory – nosiciel antygenu HBs. Zmiany w badaniu echokardiograficznym serca, pod postacią obniżonej frakcji wyrzutowej lewej komory, stwierdzono u 6 pacjentów. W jednym przypadku stwierdzono też obecność płynu w worku osierdziowym, z towarzyszącymi objawami klinicznymi. Zmiany o charakterze pneumonitis stwierdzono badaniem rtg klatki piersiowej u najmłodszej (2,5 letniej) chorej. Większość objawów miała charakter przemijający i odwracalny. Jedynie powikłania płucne wykazują tendencję do włóknienia.

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Wnioski. Obecnie prowadzona terapia HD u dzieci wymaga w wielu przypadkach stosowania czynników wzrostu, aby umożliwić realizację protokołu terapeutycznego bez opóźnień.
Częste występowanie infekcji oportunistycznych nakazuje szczególną dbałość o warunki epidemiologiczne hospitalizacji. Ze względu na stwierdzaną częstość powikłań pozaszpikowych, dotyczących różnych narządów, wskazane jest dokładne monitorowanie funkcji tych narządów w czasie i po zakończeniu leczenia.

Key words: Hodgkin's disease, children, acute complications
Słowa kluczowe: choroba Hodgkina, dzieci, ostre powikłania

Introduction

Currently over 80% of children treated for Hodgkin's disease acquire long-lasting event free survival. Therefore the survivors' good quality of life has become such an important issue [1, 2, 3, 4]. The complications of antitumour treatment may either take the form of acute toxicity – during or directly after chemo- and radiotherapy, or of late toxicity – even long after the end of oncological treatment [5, 6].

The incidence of acute side effects of chemo- and radiotherapy in children with Hodgkin's disease depends mainly on the intensity of antitumour therapy, but is also affected by the individual sensitivity of patients' tissues and organs. Acute complications predominantly involve organs characterised by a high proliferation rate and, in most cases, are entirely reversible. In such organs as the nervous system, the lungs and the heart, side effects of chemo- and radiotherapy are usually long-lasting or irreversible. Further problems arise from an increased risk of secondary neoplasm incidence in patients cured of Hodgkin's disease [7, 8].

Material and methods

The analyzed group consisted of 21 children with Hodgkin's disease, treated in the Department of Pediatrics, Hematology, Oncology and Endocrinology, Medical University of Gdańsk in the period of 1994-1998.

The characteristics of patients are shown in Tab. I.

Mean age of the group was 12 years 2 months. The majority of children (57%) were boys. 11 patients (52%) presented with clinical stage II. Nodular sclerosis (NS) histological type predominated, as it was recognised in 14 patients. Mediastinal bulky disease was stated at diagnosis in 3 children, of whom one demonstrated serious dyspnea and life-threatening signs of superior vena cava syndrome, which demanded the administration of steroids and cyclophosphamide before biopsy and histopathological examination of enlarged mediastinal lymph nodes.

Among patients presenting with clinical stage IV the extranodular sites involved were: lungs, bones, liver and spleen.

All patients were treated according to HD-95 or HD-97 protocols accepted by The Polish Pediatric Leukemia/Lymphoma Study Group. Chemotherapy cycles are summarized in Table II. In 2 children with stage IV disease, it was necessary to institute additional cycles of chemotherapy (dexaBEAM and CEP) due to their unsatisfactory clinical response to treatment. In both these cases we eventually observed a positive overall therapeutical effect.

Complete remission was achieved in 18 patients, while in the case of the remaining 3 children radiological examination revealed residual mediastinal lymph nodes. At follow-up these nodes remained stable in size. All the biochemical markers useful in assessing the activity of Hodgkin's disease proved negative.

Tab. II. Chemotherapy in patients with Hodgkin's disease

Number of cycles	4	5	6	7	8
Number of patients	3	5	5	1	7

additonal cycles applied in the treatment:
1. dexa BEAM - 1 patient
2. CEP - 1 patient

The radiotherapeutical procedures performed are presented in Table III.

Follow-up from the end of therapy was 15 mo. – 5.5 yrs.

Tab. I. Characteristics of patients with Hodgkin's disease treated between 1994-1998

Number of patients	21 boys 12 girls 9						
Age	< 5 years old 2 patients 5 – 9 years old 4 patients 10 – 14 l years old 5 patients > 14 years old 10 patients						
Remision	18/21 patients 3/21 “bulky disease” in mediastinum						
Histology	NS 14		MC 6		LP 1	LD 0	
Clinical stage	I 0	II A 7	II B 4	III A 3	III B 3	IV A 0	IV B 4
Involved non-lymphatic organs in stage IV	Lungs 2		Bones 1		Liver 1	Spleen 1	

Tab. III. Radiotherapy in patients with Hodgkin's disease

Field of radiotherapy	Number of patients
Without RTX	2
Cervical lymph nodes	4
Mediastinal field	6
Supra- and subdiaphragmatic fields	9
Involved parts of lungs	2

Results

Acute toxicities observed during active oncological treatment comprised hematological, hepatic, cardiac, infectious and pulmonary complications.

Myelosupression was the most common complication, being observed in 17 out of 21 children (80.9%). White blood cell count was affected in 13 patients (61.9%), with severe neutropenia (grade IV according to WHO scale) in most cases. It was necessary to administer hemopoietic growth factors (G-CSF or GM-CSF) in these patients. Red blood cells were transfused in 6 children (28.5%) with severe anemia. Severe thrombocytopenia (grade IV according to WHO scale) was observed only in 2 patients (9.5%). In one case a very low platelet count maintained for 30 days after the end of chemotherapy. The other patient, a 16-year-old boy with Hodgkin's disease grade II, had been previously treated for 10 years because of idiopathic thrombocytopenic purpura. His platelet count at admission was 12 G/L and so the first chemotherapy cycle dose was reduced by 50% and preceded by prednisone administered for several days. The entire oncological treatment was administered without further delays, and the patient achieved complete remission.

Infectious complications occurred in 13 children. Opportunistic infections of a mild and moderate clinical course predominated. None of them caused treatment delay.

Six out of 21 patients (28.5%) demonstrated gastrotoxic side effects of chemotherapy with predominant incidence of abdominal pain, vomiting, constipation and loss of appetite. These complications were usually observed after B-DOPA cycles, lasted for 3-7 days and, in majority of cases (5/6 patients), were of moderate degree. There was only one patient who demonstrated severe clinical signs of paralytic ileus. All these symptoms normalised after intensive therapeutic management involving parenteral nutrition and administration of gastric mucose protectors and agents normalizing intestinal peristalsis.

In 3 children (14.2%) there were mild signs of mucositis (grade I or II according to WHO scale). They disappeared approx. 7 days after the chemotherapy cycles.

Hepatotoxic side effects were predominantly manifested by an elevation of aminotransferases, without any other clinical signs. Such was the case in 6 children (28.5%), who demonstrated solitary rise in ALT and AST values of 75 to 200 U/ml. Only one patient suffered from more expressed hepatic complications with jaundice (total serum bilirubin level of 9 mg/dl) and hepatomegaly. This boy had been diagnosed to have positive serum markers of hepatitis B at admission. Liver biopsy revealed aggressive hepatitis type B, which eventually caused an 8--week delay in antitumor treatment.

Cardiological complications occurred in 6 children (28.5%). They were demonstrated in ultrasound examinations by a decrease of left ventricle (LV) ejection fraction to 53-57% (normal range: 60-80%). These disturbances proved to be entirely reversible, normalising within 2 to 6 weeks. The patients were administered coenzyme Q 10 to protect the cardiac muscle. In one patient, a 13--year-old girl, the cardiotoxic complications manifested differently. She was diagnosed as stage IV HD with infiltrations of the left lung. Because of incomplete remission after conventional chemotherapy, she was additionally administered one cycle of dexaBEAM chemotherapy and underwent radiotherapy covering mediastinal lymph nodes and left lung infiltrations. Eventually clinical remission with a residual mass in mediastinum was achieved in this patient. However, the oncological treatment resulted in clinical signs of circulatory failure, which were observed directly after the end of therapy. Consecutive ultrasound examinations demonstrated a gradually increasing pericardiac effusion. Administration of non-steroid anti-inflammatory drugs brought no improvement. However a 2-month therapy with steroids resulted in the disappearance of pericardial exudative. At present, 2 years after the end of therapy, the patient remains in remission and in good clinical state. Her ultrasound examinations show only a small amount of fluid in the pericardium.

Pulmonotoxicity occurred only in one child, the youngest of our patients (2 yr. 3 mo. old at the moment of diagnosis of HD stage IIA). Directly after the end of therapy, the girl demonstrated clinical and radiological signs of interstitial pneumonitis resistant to multiple antibiotics. Infectious etiology, involving opportunistic infections, was excluded. We observed a very good response to steroid therapy with complete normalization of clinical signs and nearly entire resolving of radiological abnormalities. The remaining radiological changes visible in the inferior lobes of both lungs have been interpreted as fibrosis, which, to the best of our knowledge, may be connected with bleomycin administrated to this patient.

Discussion and conclusions

Acute toxicities in children undergoing active treatment of Hodgkin's disease are mainly reversible, but in some cases may cause delays in the realization of chemotherapeutical protocol. It was observed in our analysis that severe myelosupression was the most common acute side effect of chemotherapy, but eventually proved to be short-lasting and entirely reversible. We have observed that the administration of colony stimulating factors shortened the period of neutropenia in our patients, which is in unison with the reports of other authors [9, 10, 11].

One must stress the high incidence of opportunistic infections in the analyzed group. This implies the necessity of providing adequate epidemiological conditions and prophylactics of contacts with contagious diseases throughout treatment.

Cardiotoxic complications may result from both anthracyclin administration and radiotherapy of mediastinal lymph nodes [12, 13, 14]. Since these factors may cumulate, it seems advisable to monitor patients in order to reveal early, clinically mute cardiotoxic side effects. The pericardial exudative, which was observed in one patient did not cause any signs of cardiac tamponade and proved entirely reversible. However, there are well-known case reports on exudative pericarditis resistant to treatment and of life-threatening severity.

Pulmonary complications usually develop as a late toxicity, and are usually related to bleomycin administration. We suggest that a younger age of patients (<5 years of age) may be an additional risk factor of pulmonotoxicity.

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