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Multiple complications and the effect of chemotherapy in a 16-year-old girl with mixed phenotype acute leukemia

Mnogość powikłań a powodzenie terapii przeciwnowotworowej u 16-letniej dziewczynki z ostrą białaczką o mieszanym fenotypie

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Key words

complications, chemotherapy, mixed-phenotype acute leukemia, pseudomembranous enterocolitis

Słowa kluczowe

powikłania, chemioterapia, ostra białaczka o mieszanym fenotypie, rzekomobłoniaste zapalenie jelit

Summary

Introduction. Mixed-phenotype acute leukemia is a rare variant of the malignant process of the bone marrow, which forms in terms of incidence of 2-5% of all cases of leukemia. Finding multiple lines of blasts in the bone marrow is associated with a worse prognosis. The problem is the choice of the appropriate chemotherapy.

Aim. The study presents a case of a child with mixed phenotype acute leukemia and many complications, which affected the course and modification of therapy.

Case report. A 16-year-old, otherwise healthy girl was diagnosed with mixed-phenotype acute leukemia. The diagnosis was based on clinical symptoms, laboratory tests and analysis of bone marrow. Consequently, ALL protocol (ALL-IC 2009) was chosen for treatment. During the first protocol of treatment the patient suffered from diabetes and progressive liver failure. After the second phase of treatment the patient complained of oral mucositis, zoster and aplastic anaemia. The severe pseudomembranous enterocolitis was occurred during the protocol II. Due to this complication, chemotherapy was discontinued. The results of mielogram showed the presence of cell population phenotype similar to the phenotype of myeloid blasts and lack of B lymphocyte precursor cells phenotypes. It was decided to start maintenance therapy according to AML protocol.

Conclusions. This case is an example of a difficult therapy, in which multiple complications interfere with chemotherapy. Severe side effects lead to interruptions in treatment, prolonged hospitalization, affect the outcome and the psyche of children, so it is very important to prevent side effects, if it is possible.

Streszczenie

Wstęp. Ostra białaczka o mieszanym fenotypie to rzadka postać ostrej białaczki, w której rozrostowi nowotworowemu ulegają dwie linie komórkowe – limfo- i mieloidalna. Taka postać choroby wiąże się ze złym rokowaniem i wymaga stosowania agresywnej chemioterapii.

Cel pracy. Analiza wpływu zdarzeń niepożądanych na efekt terapii przeciwnowotworowej.

Opis przypadku. U szesnastoletniej, dotychczas zdrowej dziewczynki na podstawie objawów klinicznych, badań laboratoryjnych i analizy szpiku kostnego zdiagnozowano ostrą białaczkę limfoblastyczną linii pre-B i mieloidalną. Zdecydowano wdrożyć chemioterapię według schematu jak dla ostrej białaczki limfoblastycznej wysokiego ryzyka (ALL-IC 2009). W czasie pierwszego protokołu leczenia u dziewczynki pojawiły się cukrzyca i postępująca niewydolność wątroby.

W kolejnych etapach terapii doszło do wystąpienia martwiczego zapalenia błony śluzowej jamy ustnej, półpaśca oraz głębokich aplazji szpiku. Chemioterapię przerwano w 8. dobie protokołu II ze względu na ciężką postać rzekomobłoniastego zapalenia jelit. Obecnie badanie szpiku wykazało narastający poziom choroby resztkowej linii mieloidalnej. Rozpoczęto leczenie podtrzymujące remisję zgodnie z protokołem dla AML (ang. *acute mieloblastic leukemia*).

Wnioski. Ten przypadek jest przykładem trudności terapeutycznych z powodu licznych powikłań. Ciężkie objawy uboczne przedłużają hospitalizację, wpływają na wyniki leczenia oraz stan psychiczny dzieci.

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INTRODUCTION

Mixed phenotype acute leukemia (MPAL) is a rare variant of hematologic malignancies and the incidence is 2-5% of all cases of leukemia. Presence of multiple lines of blasts in the bone marrow is associated with a worse prognosis. The problem is the choice of the appropriate chemotherapy. Currently, protocol treatment for acute lymphoblastic leukemia is recommended (1) (fig. 1).

The study presents a case of a child with mixed phenotype acute leukemia and side effects of chemotherapy, which caused the modification of treatment.

CASE PRESENTATION

Sixteen, previously healthy girl were examined by a general practitioner in January 2012 due to fever, weakness, an enlarged cervical lymph nodes and rashes on the skin of the abdominal area for two days. The blood test was performed and pancytopenia was found (tab. 1) and the girl was admitted to the Department of Pediatric Hematology, Oncology and Transplantation in Lublin.

Table 1. Results of first complete blood counts.

WBC	2.20 x $10^3/\mu l$
RBC	2.49 x $10^6/\mu l$
HGB	8.6 g/dl
HCT	24.2%
PLT	49 x $10^3/\mu l$

Abnormalities in peripheral blood resulted in bone marrow examination which showed the presence of 72.8% blast cells. Immunophenotype revealed 14.6% of pre-B lymphoid lineage and 34.8% of myeloid lineage. Chromosomal abnormalities in cytogenetic analysis, as well as BCR/ABL and MLL rearrangements were not found (FISH method). The patient was diagnosed as having mixed phenotype acute leukemia and chemotherapy according to the protocol ALL-IC BFM 2009 was started. Due to the age, difficult therapeutically leukemia phenotype and poor response to treatment in protocol I (on day 15 bone marrow blasts: 10.8%), the patient was qualified at high risk group (HR).

During treatment, many complications were observed (tab. 2). On day 15 of steroids therapy, diabetes (glucose – 171 mg/dl) was diagnosed and insulin was applied. On day 27 of chemotherapy, icterus was observed during physical examination. Liver functions were marked and an increase of transaminases and bilirubin (total bilirubin – 7.36 mg/dl; ALT – 1258 U/l; AST – 575 U/l; GGT – 636 U/L) were found. During the ultrasound hepatomegaly with steatosis symptoms were observed. Progressive liver failure was the cause of a three-day break in the administration of chemotherapy and new hepatoprotective treatment. This complication delay a planned course of chemotherapy for 2 weeks.

During the first HR1 block the girl complained of severe oral cavity pain and stage IV of oral mucositis was diagnosed. Leucopenia (0.05 x $10^3/\mu l$) was observed. Due to severe weakness and fever parenteral nutrition, broad-spectrum antibiotics and morphine were used. Episodes of bone marrow aplasia recurred after all HR block. During the second HR1 block the girl reported increased thirst and polyuria. Glucose was marked – 750 mg/dl. Large doses of insulin were given, resulting in normalization of glucose level. After the second

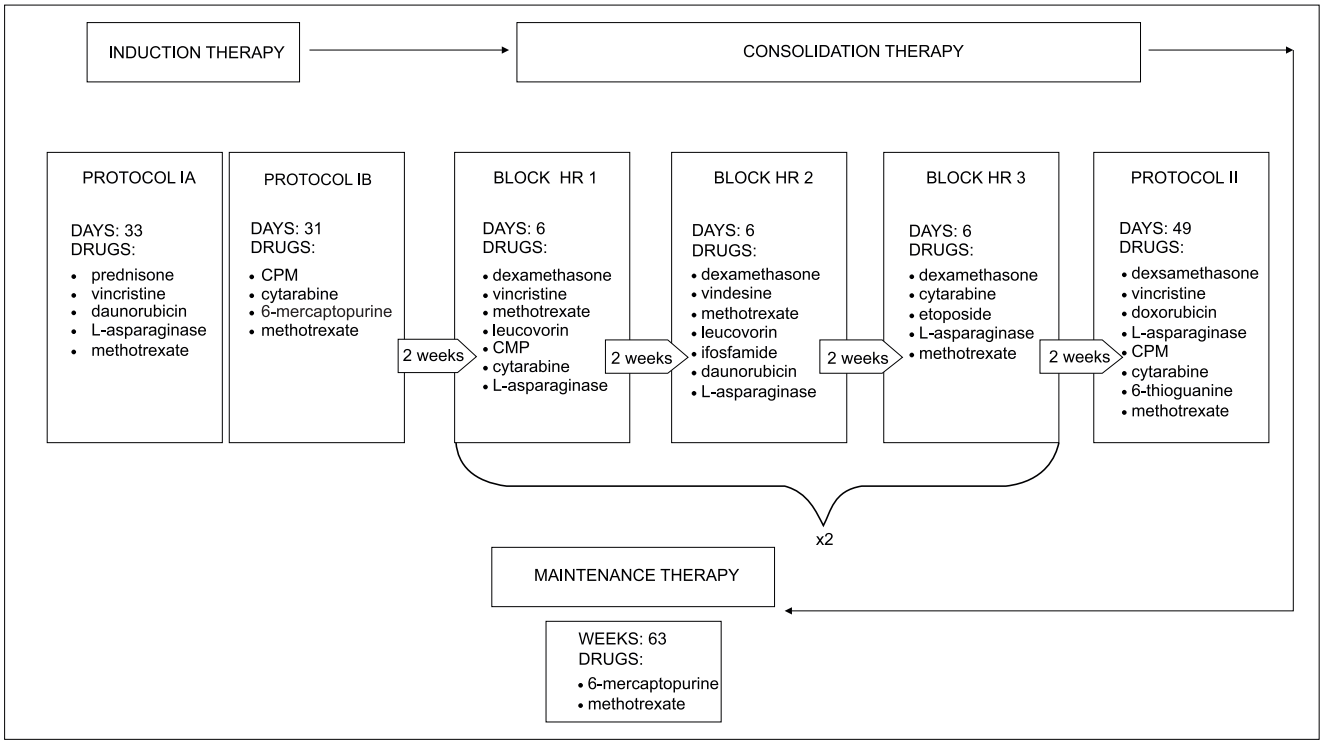

Fig. 1. Treatment scheme as per protocol ALL-IC 2009.

Table 2. Complications at consequtive stage of treatment.

STAGE OF TREATMENT	PROTOCOL I	I BLOCK HR1	I BLOCK HR2	I BLOCK HR3	II BLOCK HR1	II BLOCK HR2	II BLOCK HR3	PROTOCOL II
COMPLICATIONS	– steroid diabetes – progressive liver failure	– oral mucositis – marrow aplasia	marrow aplasia	marrow aplasia	– diabetes – marrow aplasia	– zoster – marrow aplasia	marrow aplasia	pseudomembranous colitis

HR2 block Herpes zoster infection was diagnosed and antiviral therapy with acyclovir started.

On day 8 of the protocol II, very strong abdominal pain and diarrhea with blood were observed. The tests performed for rotavirus, adenovirus and *Clostridium difficile* were negative. The blood examination showed pancytopenia and elevated CRP. Gastroscopy and colonoscopy were performed. Both the macroscopic image and histopathological analysis of intestinal mucosa sample clearly indicated pseudomembranous colitis. Oral metronidazole, vancomycin and intravenous cephalosporin, ciprofloxacin and glucocorticoids ware applied. After two weeks of treatment, control colonoscopy showed regression of inflammatory changes (fig. 2). Due to this complication, chemotherapy was discontinued.

The results of mielogram showed the presence of cell population phenotype similar to the phenotype of myeloid blasts and lack of B lymphocyte precursor cells phenotypes. It was decided to start maintenance therapy according to AML protocol.

DISCUSSION

Mixed phenotype acute leukemia is a rare, prognosis is poor and it is difficult to choose therapy.

Mejstrikova et al. studied 693 children in the Czech Republic diagnosed with acute leukemia. Among them was a small group of patients with mixed phenotype leukemia. An attempt was made to determine the suitability of this type of leukemia. The presence of the Philadelphia chromosome was observed more frequently in these patients. They also observed that therapy according to ALL protocol is more effective than AML protocol (2).

Al-Seraihy et al. conducted a study of 27 children with biphenotypic leukemia. In these cases, chemotherapy was applied according to acute lymphoblastic leukemia regimen with a good result – 73.5% of the patients were in complete remission. During the therapy increased adverse events were not noted, and the prognosis was defined as comparable to a group of high-risk acute lymphoblastic leukemia and more favorable than in the case of acute myeloid leukemia (3). In the case analysed in this study, despite the fact that the process scheme was the same the complete remission was not achieved.

Gao et al. have attempted to find favorable prognostic factors in the course of mixed phenotype leukemia. They found that young age, normal karyotype and the induced therapy as for lymphoblastic leukemia are factors that increase the chances of effective treatment and remission. Adults, in which karyotype the Philadelphia chromosome occured chances of recovery are reduced (4). Despite the relatively young age, no chromosomal mutation and inclusion of proper treatment protocol, it is difficult to talk about results of therapy in the analysed patient due to many complications.

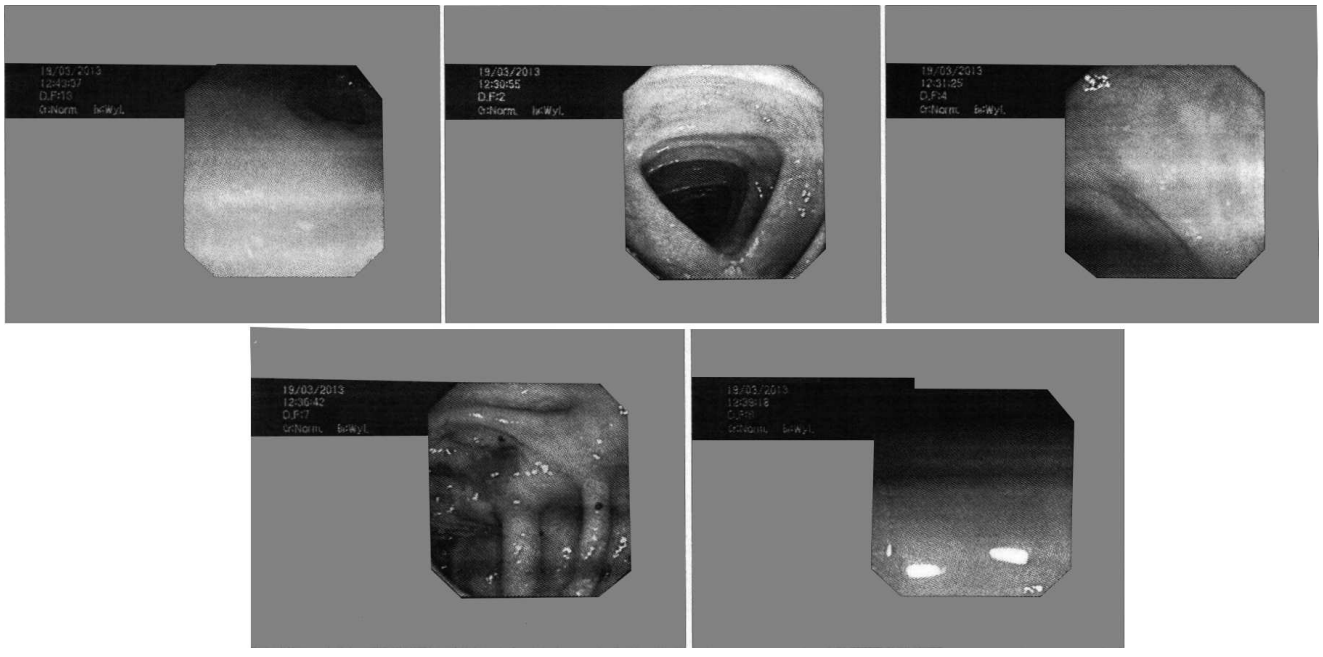

Fig. 2. Endoscopic examination: mucous membrane in recovery.

Bachir et al. in the study analysed 1264 patients diagnosed with acute leukemia. 12 of these children with mixed phenotype leukemia. Based on a large research group he attempted to define the connection between the phenotype of leukemia and therapeutic effect. No correlation in this area was found (5).

Koltin et al. studied 363 patients treated for acute leukemia according to regimen for acute lymphoblastic leukemia. As a criterion indicating the occurrence of drug-induced diabetes he accepted an occurence within two days of induction therapy blood glucose values exceeding 200 mg/dl. On that basis he diagnosed diabetes in 15.7% of patients. Then identified the factors predisposing to the development of this complication – it was the age of above 10 years of age and diseases of the central nervous system (6).

There are numerous publications indicating that diabetes can be induce not only glucocorticosteroids, but also L-asparaginase used in the protocol ALL-IC 2009 (7, 8).

Roberson et al. analysed the risk factors predisposing to diabetic ketoacidosis during chemotherapy. The age above 10 years was a significant factor (9). In Weiser et al. studies, 103/278 patients treated for acute lymphoblastic leukemia were diagnosed with diabetes during induction therapy. Among these patients a worse response to further treatment was noted, increased mortality and increase of the probability of complicating infections (10).

Patient described in this study, elevated glucose level was observed from the start of induction therapy. Her age was a definite risk factor for this complication, and frequent infections – a potential effect.

Mucositis is one of the most common complications of immunosuppressive therapy. This may be the result of bacterial, fungal and viral infections (11).

Figliolia in their study indicates that the risk of inflammatory lesions in the mouth in the course of chemotherapy increases with the age of the child and the level of neglect of hygiene (12). Mucositis in this patient was associated with the inclusion of parenteral nutrition, high doses of morphine and antibiotics, and longer hospitalization.

The most serious complication in the presented case was infection of *Clostridium difficile* and consequently – pseudomembranous colitis. The main risk factors predisposing to the development of the disease are prolonged hospitalization, age over 65 years, multidrug antibiotic therapy and immunosuppressive therapy (13). In this case constant hospitalization, antibiotics, chemotherapy triggered this infection.

CONCLUSIONS

This case is an example of a difficult therapy, in which multiple complications interfere with chemotherapy. Severe complications lead to interruptions in treatment, prolonged hospitalization, affect the outcome and the psyche of children, so it is very important to prevent side effects, if it is possible.

BIBLIOGRAPHY

1. Weinberg OK, Arber DA: Mixed-phenotype acute leukemia: historical overview and a new definition. Leukemia 2010 Nov; 24(11): 1844-1851.
2. Mejstrikova E, Volejnikova J, Fronkova E et al.: Prognosis of children with mixed phenotype acute leukemia treated on the basis of consistent immunophenotypic criteria. Haematologica 2010 Jun; 95(6): 928-935.
3. Al-Seraihy AS, Owaidah TM, Ayas M et al.: Clinical characteristics and outcome of children with biphenotypic acute leukemia. Haematologica 2009 Dec; 94(12): 1682-1690.
4. Gao Ch, Sands AM, Sun J: Mixed Phenotype Acute Leukemias. NAJ Med Sci 2012; 5(2): 119-122.
5. Bachir F, Zerrouk J, Howard SC et al.: Outcomes in Patients With Mixed Phenotype Acute Leukemia in Morocco. J Pediatr Hematol Oncol 2013 Apr 24.
6. Koltin D, Sung L, Naqvi A, Urbach SL: Medication induced diabetes during induction in pediatric acute lymphoblastic leukemia: prevalence, risk factors and characteristics. Support Care Cancer 2012 Sep; 20(9): 2009-2015.
7. Mondal R, Nandi M, Tiwari A, Chakravorti S: Diabetic ketoacidosis with L-asparaginase therapy. Indian Pediatr 2011 Sep; 48(9): 735-736.
8. Wang H, Li D, Li JT et al.: Side effects of L-asparaginase during therapies for remission induction and maintenance in children with acute lymphocytic leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2009 Jun; 17(3): 739-741.
9. Roberson JR, Raju S, Shelso J et al.: Diabetic ketoacidosis during therapy for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2008 Jun; 50(6): 1207-1212.
10. Weiser MA, Cabanillas ME, Konopleva M et al.: Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate-cytarabine regimen. Cancer 2004 Mar 15; 100(6): 1179-1185.
11. Subramaniam P, Babu KL, Nagarathna J: Oral manifestations in acute lymphoblastic leukemic children under chemotherapy. J Clin Pediatr Dent 2008 Summer; 32(4): 319-324.
12. Figliolia SL, Oliveira DT, Pereira MC et al.: Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients. Oral Dis 2008 Nov; 14(8): 761-766.
13. McCollum DL, Rodriguez JM: Detection, Treatment and Prevention of *Clostridium difficile* infection. Clinical Gastroenterology and Hepatology 2012; 10: 581-592.

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