CASE REPORT

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Treatment-related mortality in the course of acute lymphoblastic leukemia – case report

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Abstract

The treatment of acute lymphoblastic leukemia (ALL) in children has become increasingly effective over the years. Currently, the cure rate is about 90%. This has become possible due to the use of combinations of appropriate chemotherapeutics in very high, often maximum doses. This is associated with the occurrence of so-called treatment-related mortality (TRM), the main cause of which is infections. The case report is presented of a 12-year-old patient who contracted a respiratory syncytial virus (RSV) infection during the consolidation phase of ALL treatment. The course of the infection was so severe that despite intensive antimicrobial treatment and a stay in an intensive care unit (ICU) the patient died. This indicates the absolute necessity of constant monitoring of a patient's condition and consideration of early inclusion of antimicrobial prophylaxis, especially in patients at risk.

Key words

children, acute lymphoblastic leukemia, Respiratory Syncytial Virus Infections

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for 25% of all cancers among paediatric patients [1]. It accounts for one-third of newly diagnosed cancer cases with an incidence rate of between 10–50 cases per 100,000 children per year [2]. For many years there has been a steady improvement in ALL treatment outcomes, primarily related to the use of new targeted therapy programmes. Currently, the cure rate for ALL with appropriately combined chemotherapy is over 90%. However, this involves the use of drugs in very high doses [3]. The afore-mentioned intensification of treatment is associated with the observation of so-called treatment-related mortality (TRM). This occurs in 2–4% of paediatric patients with ALL, with infections being the main cause. It is also worth noting that the incidence of TRM is similar to the rate of relapse after treatment in low-risk (LR) patients [4]. Consequently, adequate prevention and treatment of infection during chemotherapy poses a major challenge for haematologists.

The aim of this study is to highlight the relevance of the issue of TRM caused by infection during ALL treatment through a case report.

CASE REPORT

The patient, a 12-year-old girl, attended the Clinic in May 2021 because of weakness and subfebrile states that had lasted for two weeks. The results of some tests from the day of admission are shown in Table 1. Other laboratory test results, including urea, creatinine and uric acid levels, remained within reference norms. The presented results, including several increases in the number of white blood cells, lymphocytes and monocytes and higher levels of lactate dehydrogenase, are a typical laboratory picture of ALL.

Table 1. Results of some of the patien's laboratory tests on day of hospital admission

Parameter	Result	Range of reference
Leukocytes [10^3/µl]	87.71	4.1–8.9
Erythrocytes [10^6/µl]	4.72	4.1–5.2
Hemoglobin [g/dl]	12.2	12.2–14.8
Platelets [10^3/µl]	264	140–420
Neutrophils [10^3/µl]	10.59	2.5–7
Lymphocytes [10^3/µl]	57.42	0.8–4
Monocytes [10^3/µl]	19.55	0.2–1.2
Eosinfiles [10^3/µl]	0.19	0–0.4
Basophiles [10^3/µl]	0.14	0–0.1
LDH [U/l]	466	0–308
AST [U/l]	23.14	0–51
ALT [U/l]	7.91	0–23
CRP [mg/dl]	1.11	0–0.5
D-dimers [ng/ml]	2548	<500

AST – aspartate aminotransferase; ALT – alanine aminotransferase; CRP – C-reactive protein; LDH – lactate dehydrogenase

A chest X-ray showed no pathology, an abdominal ultrasound showed an enlarged spleen. A bone marrow aspiration biopsy was performed, which showed 80.3% B lymphocyte precursor cells with an abnormal phenotype. On the basis of cytomorphological, cytoenzymatic and cytometric

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examination, acute lymphoblastic leukemia (ALL pre-B) was diagnosed and chemotherapy was started according to Protocol I according to the AIEOP-BFM-ALL-2017 programme. Genetic testing by RT-PCR showed the presence of *BCR-ABL* fusion gene – Philadelphia chromosome. The decision was made to continue treatment according to EsPhALL2017/COGAALL1631 with tyrosine kinase inhibitor (imatinib) at a dose of 340 mg/m^2 from day 15 of the therapy. On that day, the response therapy to was unsatisfactory, with 64.9% blast cells in the bone marrow. On day 33, minimal residual disease (MRD) was measured at $8x10^{-2}$. After completion of IB Induction, MRD result was $<1x10^{-4}$, which qualified the patient for the SR group. The girl was randomized to Arm A according to the EsPhALL2017 protocol. Treatment was complicated by pancytopenia, coagulation abnormalities, hypoalbuminaemia, toxic liver disease, hypertriglyceridaemia, electrolyte abnormalities, and infection.

In September 2021, the patient received Consolidation Block 1 SR Arm A according to the EsPhALL2017 protocol. At that point, a bone marrow biopsy revealed 3.65% blast cells. On the first day of Block 1, the patient received a high dose of methotrexate (5 g/m^2). She had complications of III^o stomatitis, gastrointestinal bleeding, *C. difficile* infection, features of renal failure, toxic liver disease, water-electrolyte and acid-base disorders. Block 1 was discontinued on day 4; she received methotrexate, vincristine and 3 doses of cyclophosphamide. As a result of the previously complications, imatinib was discontinued, to which it was returned after a 20-day break. In November 2021, the patient was admitted for follow-up Block 2 SR Arm A according to EsPhALL2017. Polyneuropathy and cachexia were diagnosed. It was decided to discontinue imatinib in 6th day. In that day, there was also an allergic reaction to L-asparaginase (redness, rash, vomiting).

In December 2021, the patient received Block 3 SR Arm A according to EsPhALL2017 with good tolerance. Five days after the end of the Block, she began to have fever and was tested positive for Respiratory Syncytial Virus (RSV). Dexamethasone, immunoglobulins and budesonide inhalations were administered 4 times per day. The patient began to develop features of respiratory failure – oxygen saturation 88%. A significant deterioration of laboratory parameters was observed. Some of the results are shown in the Table 2. Reduced oxygen partial pressure in arterial blood gasometry was a specific marker of respiratory failure, and pancytopenia in peripheral blood count was an expression of impaired bone marrow function in the course of treatment and RSV infection (especially neutropenia and thrombocytopenia).

Table 2. Results of some of the patient's laboratory tests after diagnosis of RSV infection

Parameter	Result	Range of reference
Leukocytes [10^3/µl]	0.11	4.1–8.9
Erythrocytes [10^6/µl]	4.02	4.1–5.2
Haemoglobin [g/dl]	11.6	12.2–14.8
Platelets [10^3/µl]	45	140–420
pH	7.37	7.35–7.45
pCO_2 [mmHg]	34.6	34–36
pO_2 [mmHg]	34.9	80–100

pCO_2 – partial pressure of carbon dioxide in arterial gas blood test; pO_2 – partial pressure of oxygen in arterial gas blood test.

The patient was administered passive oxygen therapy, initially at a low flow rate of 2 liters per minute (LPM) and progressively increased to 5–6 LPM. The bedside chest X-ray showed decreased aeration of the left lung with the presence of oval opacifiction – parenchymal thickening, more consolidated lesions in the upper field (45 mm in diameter), and smaller nodular thickening in the middle field (15 mm in diameter). Meropenem, vancomycin and clarithromycin were included in the treatment. After a temporary improvement, the patient's condition gradually deteriorated, as a result of which the oxygen flow rate was increased to 9 LPM. Despite this, a saturation higher than 70–72% could not be achieved. The patient was transferred to the intensive care unit (ICU), where doctors found a saturation level of 98% with high-flow passive oxygen therapy, which gradually decreased to 73%. Physical examination revealed deterioration of consciousness, peripheral cyanosis, pale and marbled skin, tachypnoea, exaggerated vesicular breath sounds, and capillary refill time of >3s. The patient was therefore intubated and mechanical ventilation in Adaptive Support Ventilation (ASV) mode was used. The patient's condition began to be critical – declines in systemic pressure with microcirculatory hypoperfusion were noted. She required the intensification of fluid therapy with the introduction of catecholamines. Pathological breathing pattern, the so-called 'gasping' appeared. Despite treatment, the girl died in the course of circulatory failure 7 months after the diagnosis of proliferative haematopoietic disease.

DISCUSSION

Treatment of ALL according to the basic regimen of the AIEOP-2017 Poland Programme is based on 4-stage chemotherapy (induction, consolidation, re-induction, maintenance treatment) with maximum doses of drugs, such as anthracyclines, vincristine, cyclophosphamide, 6-mercaptopurine or methotrexate. The above chemotherapeutics are selected according to the phase of treatment [5]. The use of high doses of drugs is associated with increased risk to the patient, including TRM. The most important causes of TRM include infection related mortality (IRM), bleeding and organ failure. The above conditions, by definition, cannot be induced by the disease itself, but only by therapy [4]. The highest risk of infection is during the induction and reinduction phases, due to the intensity of therapy. Infections, primarily of the ear and respiratory tract, mainly of viral origin, are also observed in the consolidation phase [6]. TRM occurs in about 2–4% of patients treated for ALL [7,8]. Oskarsson et al. in their study in a group of patients with ALL, recorded 52 treatment-related deaths in the Nordic countries: Denmark, Finland, Iceland, Norway and Sweden, between 1992–2012. Of this group, 38 deaths were due to infections: 15 bacterial, 10 viral (none RSV) and 6 fungal [9]. Lund et al. indicated that TRM affected 88 patients out of 2,375 paediatric patients with ALL (1992–2008, Nordic countries listed above) [10]. The problem is much more common in developing countries, as the researchers themselves point out. Ul-Ain et al. in a single-centre study from Pakistan, reported 742 patients in 2017–2018, of whom 247 (58.3%) died. In 126 patients, the cause of death was sepsis, in 54% of cases, of respiratory origin [11]. Kowalczyk et al. in a Polish study conducted between 2002–2011 in a group of 1875 paediatric patients with ALL, reported 268 deaths, of which only 65 were

due to TRM [12]. Zawitkowska et al. in a study conducted between 2012–2017 in a group of 1,363 paediatric patients with ALL, reported 28 IRM deaths, 5 of which were caused by viral infection (1 by RSV) [13]. The problem of TRM affects not only haematology patients, but also all oncology patients. Loeffen et al. (203–2012) reported 81 deaths classified as TRM, 43 of them as IRM in a group of 1,764 oncology patients [14].

The cited findings illustrate that the problem of IRM is rare in developed countries, although it continues to be a significant challenge for physicians. TRM can occur in all phases of treatment, but most frequently involves the induction phase (59–65%) and maintenance treatment (24%) [7,8]. Gupta et al. noted that IRM predominates during maintenance treatment, but a higher proportion of TRM related to bleeding or metabolic causes, is observed in the initial phases [7]. The treatment of the patient in the presented case study was in the consolidation phase. At this stage, it accounts for only 17% of TRM deaths. [8]. Predictive factors for the development of TRM are female gender, white race, concomitant Down syndrome, HR status, malnutrition, high output leukocyte count, reduced haemoglobin, low platelet count, neutropenic fever, hepatotoxicity, and longer travel time to a tertiary referral hospital. The strongest factors of those mentioned above are Down syndrome, neutropenic fever and toxic liver damage. [4,6,7,8]. People with Down syndrome show increased sensitivity to methotrexate and anthracyclines [9]. The patient in the case study described had female gender, white race, malnutrition, in the HR group, elevated leukocyte counts and toxic liver damage. Moreover, O'Connor et al. and Inaba et al. agree that the use of high doses of dexamethasone, especially in combination with anthracyclines during the induction phase, is associated with a higher incidence of infectious complications, including sepsis. However, most of the cases they discussed ended in full recovery, indicating the validity of appropriate antimicrobial prophylaxis from the first stages of therapy [4,6].

The main pathogens causing infections in children during ALL treatment are bacteria (53% of children), fungi (20%) and viruses (18–35%) [15,16]. Among bacteria, the most common infections resulting in IRM, according to O'Connor et al., were caused by Gram-negative bacteria (64%), and of these – P. *aeruginosa* (22%) and *E. coli* (20%) [4]. In a Polish study, Styczyński noted that Gram-positive bacteria caused the most frequent infections (57.5%), mainly by the bloodborne route (71.3%) [15]. The fungal species most frequently infecting patients with ALL are *Aspergillus* (67%) and *Candida* (25%) [4]. Among viruses, COVID-19 (23%), rhinovirus (18%) and RSV (14%) were the most frequently observed in recent years (from 2020). In the pre-pandemic era (2018–2019), the most common infections were caused by adenoviruses (49%), rotavirus (32%) and VZV (8%) [16]. In the case of IRM, the most common viruses isolated were adenoviruses (43%), VZV (29%) and RSV (28%), accounting for 12% of deaths due to infections in the course of ALL [4].

Therefore, adequate prevention and treatment of infections in patients undergoing chemotherapy is an extremely important issue. In patients with ALL, especially those at risk (e.g., those with Down syndrome), antibiotics and antifungal agents should be considered, starting from the induction phase. Effective regimens include vancomycin, meropenem and fluoroquinolones (especially levofloxacin). In malnourished patients, those with hypogammablobulinaemia or frequent recurrent viral infections, intravenous immunoglobulins can be used [6]. Close monitoring of the patient's condition and appropriate modification of chemotherapy are also fundamental.

CONCLUSIONS

TRM is a major problem in the treatment of paediatric patients with ALL. The new treatment standards are associated with significantly better outcomes, but infections during the course of therapy increase mortality. For this reason, infections, primarily bacterial, although also viral are among the key factors affecting patient outcomes and prognosis, and eliminating IRM would help improve overall survival. Therefore, early prophylactic antimicrobial measures (antibiotics, such as levofloxacin or antifungal agents) should be taken in at-risk groups (patients with Down syndrome, HR status, significant laboratory abnormalities, organ failure).

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