

Early complications of induction therapy in children with acute lymphoblastic leukemia treated according to the ALL IC-BFM 2002 regimen

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Introduction. The percentage of survivors of childhood malignancies has been steadily increasing up to 80% at present. Despite of the progress in prophylaxis and treatment of early and late side effects, the latter still deteriorate the results of ALL therapy. Therefore, to assure further improvement of treatment results and to reduce the risk of life threatening side effects, further analysis and identification of characteristic early and late complications is needed.

Patients and methods. Sixty children (28 boys, 32 girls) with ALL diagnosed and treated in the Department of Pediatric Oncology, Hematology and Transplantology, University of Medical Sciences in Poznań, over the period between October 2002 and March 2006 were included. Median age at diagnosis was 5 years. Infectious and toxic side effects were graded from 0 to IV according to WHO exact criteria.

Results. Early complications, including infectious, toxic and corticosteroid-related, were observed in 73.3% children. Infection was diagnosed in 54.5% patients, in 54.2% children the diagnosis was only clinically documented, in 45.8% cases infection was also confirmed by microbiological tests. Neutropenic fever of unknown origin occurred in 18.6% children. There was one (2.2%) non-relapse death related to viral infection complicated by the Waterhouse-Friedrichsen syndrome. Toxic stomatitis was diagnosed in 43.2% of cases and liver toxicity in 27.3% of cases, diarrhea in 27.3% patients, whilst nausea and vomiting in 6.8% patients. Coagulopathy (thromboembolic and haemorrhagic episodes) was diagnosed in 6.8% children. The mean glucose level was 82.54 ± 13.89 mg/dl before the treatment, whilst 99.01 ± 45.39 mg/dl after protocol I. Three (6.8%) patients were diagnosed with hyperglycaemia after protocol I. The mean Body Mass Index (BMI) level measured after protocol I was higher than before the treatment, whereas the potassium levels measured after protocol I were significantly lower than the level before the treatment. In 83.7% children complications significantly prolonged remission induction therapy. The age group where complication occurred in 90% was group of patients between 5 and 10 years of age. The frequency of complications in all risk groups were similar and reached 71.4% in the SR-group, 70.4% in the IR-group and 73.7% in the HR-group.

Discussion. This study presents the most common complications during remission induction of ALL therapy according to the ALL IC-BFM 2002 protocol. The spectrum of observed side effects does not differ markedly from those obtained recently by other groups. Nevertheless, in order to achieve better outcomes in childhood ALL in the future prompt and accurate analysis of early complications may provide better supportive care in this group of pediatric patients.

Key words: ALL, childhood, complications, infection

Introduction

The percentage of survivors of childhood malignancy has been steadily increasing up to 80% at present. This expanding population of childhood malignancy survivors mandates better characterization of the side effects of the oncological treatment in order to improve our understanding of their impact on early and long-term treatment results [1].

Acute lymphoblastic leukemia (ALL) represents about 25-30% of malignancy in children and thus is the most common one in childhood. The prognosis of ALL has improved greatly over the last decades. More than 95% of patients achieve complete remission (i. e. blast cells <5% in the bone marrow and disappearance of clinical symptoms related to the disease) and about 80% are expected to be cured with current chemotherapy regimens [2, 3]. Nevertheless, despite of the progress in prophylaxis and treatment of early and late side effects, they still deteriorate the results of ALL therapy. Therefore, to assure the further improvement of treatment results and reduce the risk of life threatening

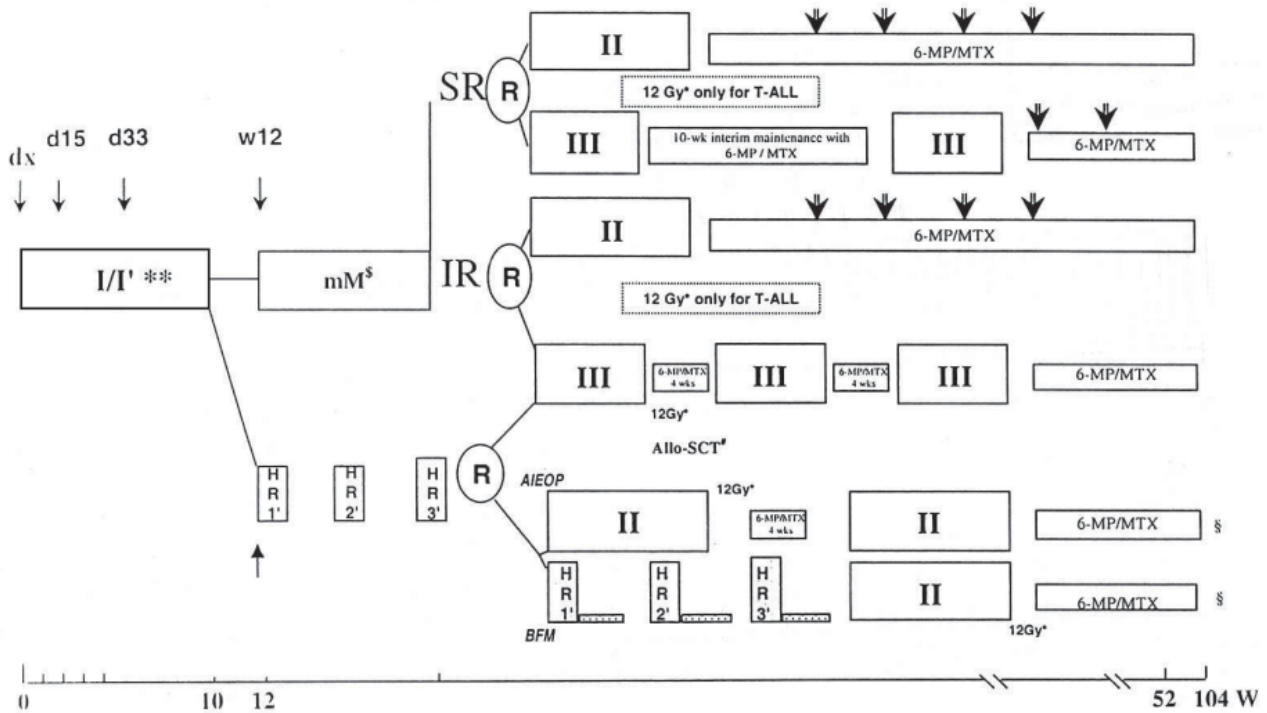


Figure 1. The outline of the ALL IC BFM-2002 regimen [5]

side effects, further analysis and identification of characteristic early and late complications is needed.

In Poland, since November 2002, children with ALL are treated according to the ALL IC-BFM 2002 regimen (Figure 1) [4]. The intensity of treatment is stratified according to the following risk factors: age, leukocyte count, translocations $t(9;22)$ (BCR/ABL+) and $t(4;11)$ (MLL/AF4+) as well as response to pretreatment with corticosteroids and time to complete hematological remission [5]. However, the induction therapy, which is the most intensive part of the regimen, is the same in all the three risk groups, i.e. in the standard, the intermediate and the high risk group.

The aim of this study was to analyze the infectious, toxic and corticosteroid-related complications observed during the administration of protocol I in children with ALL treated according to the ALL IC-BFM 2002 regimen, i.e. till day +64 of treatment and to correlate them with other factors such as age at diagnosis and risk group.

Patients and methods

Patients' characteristic and treatment

Sixty children (28 boys, 32 girls) with ALL diagnosed and treated in the Department of Pediatric Oncology, Hematology and Transplantology, University of Medical Sciences in Poznań, over the period from October 2002 to March 2006 were included. Median age at diagnosis was 5 years (range: 1 – 18 years).

The patients were treated according to the ALL-IC BFM 2002 regimen and divided into three risk groups: 14 children were in the SR-standard risk group, 27 children in the IR-intermediate risk group and 19 children in the HR-high risk group. The standard risk group consisted of patients between

1 – 6 years of age with $WBC < 20,000/\mu l$ at diagnosis and with absolute peripheral lymphoblast count below 1000 per μl at day 8. of treatment. Children older than 6 years or with initial leukocytosis above $20,000/\mu l$ with a good response on day 8. of treatment were treated as the intermediate risk group. The high risk group was defined by a peripheral blast count of over 1000 per μl at day 8. of treatment and/or genetic aberrations (BCR/ABL, MLL/AF4) and/or lack of hematological remission at +33 day.

Induction therapy consists of a multidrug chemotherapy containing: vincristine, L-asparaginase, daunorubicin, cyclophosphamide, cytarabine, 6-mercaptopurine, methotrexate and prednisolone.

Treatment complication grading

Infectious and toxic side effects were graded from 0 to IV according to WHO exact criteria presented in Table I.

Statistical analysis

Wilcoxon test, paired t test and unpaired t test were used for statistical analysis.

Results

Early complications, including infectious, toxic and corticosteroid-related were observed in 44/60 (73.3%) children, 25 girls and 19 boys (Table II).

Infectious complications

Infection was diagnosed in 24/44 (54.5%) patients (grades: 1 in 17 patients, 2 in 5 patients, 3 in 2 patients). In 13/24 (54.2%) children the diagnosis was only clinically documented, in 11/24 (45.8%) cases infection was also confirmed by microbiological tests (microbiologically

Table I. Grading of infectious and toxic side effects according to acute toxicity form [5]

Grade	0	1	2	3	4
Infection	none	mild	pathogen non identified, i.v. antibiotics	pathogen indentified, i.v. antibiotics	septic shock
Fever (°C)	<38	38-39	>39-40	>40 <24h	>40 ≥24h
Vomiting (in 24h)	0	1	2-5	6-10	>10 TPN necessary
Stomatitis	none	painless ulceration erythema	painfull ulceration can still eat	painfull ulceration cannot eat	TPN required due to stomatitis
Diarrhea (stool frequency/day)	none	2-3	4-6 or night stools or light cramps	7-9 or incontinence or strong cramps	10 or bloody diarrhea or TPN required
Liver toxicity (S-ALT/S-AST)	normal for age	>N - 2.5*N	>2.5 - 5.0*N	>5.0 - 20.0*N	>20.0*N

Table II. Occurrence of early complications in ALL patients

Early complications	Number of patients (%)
Infectious complications including:	24/44 (54.5%)
clinically documented infection	13/24 (54.2%)
microbiologically documented infection	11/24 (45.8%)
fever of unknown origin	8/24 (33.3%)
Toxic complications including:	21/44 (47.7%)
toxic stomatitis	19/44 (43.2%)
liver toxicity	12/44 (27.3%)
diarrhea	12/44 (27.3%)
nausea and vomiting	3 (6.8%)
Coagulative complications	3 (6.8%)
Endocrine complications	3 (6.8%)
Circulatory complications	1 (2.2%)

documented infection). The infection was caused by Gram-positive bacteria (3/11; *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Staphylococcus hominis*), Gram-negative bacteria (3/11; *Stenotrophomonas maltophilia*, *Acinetobacter Lwoffii* and *Enterobacter cloacae*), viruses (3/11; twice *Herpes simplex virus* and *Varicella zoster virus*), fungi (2/11; *Candida albicans* and *Candida parapsilosis*). Neutropenic fever of unknown origin occurred in 8 (18.6%) children (grade 1 in 7 children, grade 2 in 1 child). Infection was accompanied by leukopenia (WBC<1*10⁹/L) in 12/24 (50%) patients. There was one (2.2%) non-relapse death related to viral infection with Waterhouse-Friedrichsen syndrome.

Toxic complications

Toxic stomatitis was diagnosed in 19/44 (43.2%) (grade 1 in 16 children, grade 2 in 3 children) and liver toxicity in 12/44 (27.3%) children (grade 1 in 7 patients, grade 2

in 4 patients, and grade 3 in 1 patient), diarrhea in 12/44 (27.3%) patients (grade 1 in 11 patients, grade 2 in 1 patient), whilst nausea and vomiting in 3 (6.8%) patients (grade 1 in 1 patient, grade 2 in 2 patients). Leukopenia without infection was observed in 7 (15.9%) children.

Coagulative complications

Coagulopathy (thromboembolic and haemorrhagic episodes) was diagnosed in 3 (6.8%) children (18., 19. and 21. day of treatment) and caused ischaemic stroke in 1 (2.2%) child.

Endocrine complications

The glucose plasma level was evaluated before treatment and after protocol I. The mean glucose level was 82.54±13.89 mg/dl before the treatment, whilst 99.01±45.39 mg/dl after protocol I, i.e. was significantly higher (n=53, p=0.001; Wilcoxon test) after the treatment. Three (6.8%) patients were diagnosed with hyperglycaemia after protocol I. In all of them normalization of hyperglycaemia was obtained after corticosteroids discontinuation. The mean Body Mass Index (BMI) level measured after protocol I was higher than before the treatment (16.68 kg/m² vs 16.08 kg/m²; p=0.0097, paired t test).

Circulatory complications

Transitional corticosteroids-related hypertension was found in 1 (2.2%) child from the HR group on day 47.

Electrolytes disturbances

The mean potassium level measured after protocol I was 4.0 mmol/L and it was significantly lower than the level before the treatment, 4.2 mmol/L (p=0.0154, paired t test).

Table III. Correlation the frequencies of complication with other factors

Frequency of complications and the age at diagnosis (p=0,03)			
1-5 years	5-10 years	10-15 years	above 15 years
14/24 (58.3%)	18/20 (90.0%)	9/11 (81.8%)	3/5 (60.0%)
Frequency of complications and the risk groups (p=0,97)			
SR-group	IR-group	HR-group	
10/14 (71.4%)	19/27 (70.4%)	14/19 (73.7%)	

Correlation between complication incidence and remission induction duration

In 36/44 (83.7%) children complications significantly prolonged remission induction therapy, i.e. for less than 14 days in 13 (30.2%) and for more than 14 days in 23 (53.5%) children (p=0.001, unpaired t test).

Correlation between complication incidence with other factors

Correlations between the frequencies of complications, age and the risk group are presented in Table III. The age group where complications occurred in 90% was group of patients between 5 and 10 years, whereas in the group of youngest patients complications occurred only in 58.3%, in children 10-15 years old complications were observed in 81.8%, and in the group of patients above 15 years 60.0%, respectively. The frequency of complications in all risk groups was similar and reached 71.4% in the SR-group, 70.4% in the IR-group and 73.7% in the HR-group (p=0.97).

Discussion

Despite the significant progress of childhood ALL therapy treatment-related complications still remain an important cause of morbidity in this group of patients. The aim of this study was to assess the type and frequency of side effects occurring in children with ALL treated according to the ALL IC-BFM 2002 regimen during the remission induction phase which is the most intensive part of ALL therapy. In the course of the study the most frequently observed complication was infection (54.5%). Similar results achieved Lex et al. [6] and Katsimpardi et al. [7]. In contrast to our analysis, Graubner et al. [8] found infectious complications in only 29% of patients during induction. Among infectious complications more frequent were only clinically documented infections (54.2%), whilst microbiologically documented infections were present in 45.8%. Another group consisted of patients presenting with FUO (18.6%). In contrast to our analysis Graubner et al. found 70% of FUO and 30%

of clinically or microbiologically documented infections. Reasons for these differences remain unclear. The predominance of Gram positive bacteremias in the group of microbiologically documented infections was reported by different studies on children with cancer [7]. This result is reported to be a probable consequence of long-dwelling intravascular devices or mucositis induced by high dose chemotherapy [8]. Finally, the frequency of death due to infectious complications during the induction phase assessed as 1.7% is comparable with other reported data [9].

Differences in steroid-related complication frequency in comparison with Kourti M. et al. [10] may result from short time (64 days) of our observation. Obesity or metabolic syndrome reported by Kourti M. [10] and Chow E. [11] as the most common corticosteroid-related complications need a longer period of time to reveal. The recorded rate of 2.2% thromboembolic events was similar to published data observed in ALL patients during steroid administration [12].

The most important conclusion is that the observed complications significantly prolonged the duration of induction therapy in over 80% of children with ALL. The delay in the day of achieving remission which is the most important prognostic factor in these patients may promote relapse occurring and cure rate decreasing in the future.

This study presents the most common complications during remission induction of ALL therapy according to the ALL IC-BFM 2002 protocol. The spectrum of observed side effects does not differ markedly from those reported recently by other groups. Nevertheless, for the future better outcomes in childhood ALL, the prompt and accurate analysis of early complications may provide with better supportive care in this group of pediatric patients.

Conclusions

1. The majority of children presented early complications during remission induction therapy. The most common complication was clinically documented infection.

2. The major observed corticosteroids-related complication was temporary hyperglycemia.
3. In the analyzed group non-relapse deaths resulting from early complications of induction therapy occurred in 2.2% of children.
4. There is no difference in frequency of complications in correlation with sex and risk group.
5. The rate of early complications is significantly higher in children at the age between 5 and 15 years than in others.
6. Complications significantly prolonged remission induction therapy, and thus may demonstrate as negative impact on long term results of the treatment.

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