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Original Paper

Toxicity, Supportive Care and Costs of two Chemotherapy Protocols for Treatment of Childhood ALL in Russia: BFM 90m and MB 91

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Since the late 1980s, polychemotherapy protocols for the treatment of childhood acute lymphoblastic leukaemia (ALL) derived from Western European and American regimens have been introduced in Russian paediatric oncology centres. Whereas treatment results were significantly improved compared with the results of former non-standard treatment strategies, the substantial toxicity of these protocols required a high standard of supportive care, and the high costs of treatment became a major problem. In 1991, a new protocol was developed with the aim of reducing toxicity and costs without affecting efficacy of the treatment. Since 1991, a single-centre study comparing the new Russian Protocol, Moscow-Berlin 91 (MB), with a modified version of the protocol ALL BFM 90 (BFM) of the Berlin-Frankfurt-Münster group was performed in Moscow to evaluate possible advantages of the new protocol under Russian conditions. The aim of the present analysis was to compare toxicity, need of supportive care and expense of both regimens (BFM, 25 pts; MB, 32 pts). Hepatotoxicity (liver enzymes), nephrotoxicity (creatinine), duration of neutropenia, and platelet transfusions were similar in both protocols. The median erythrocyte transfusion level was greater in the BFM (1000 ml/m^2) than the MB patients (505 ml/m^2, $P<0.01$), as was the length of intravenous (i.v.) antibiotic therapy (22 days BFM versus 9 days MB, $P<0.01$), treatment delays (39 days BFM versus 21 days MB, $P<0.001$), and duration of in-patient treatment (47 days BFM versus 18 days MB, $P<0.001$). Side-effects of the MB protocol occurred mainly during induction therapy. Total costs (mean cost/person/m^2 body surface) of treatment including supportive care were 1.73-fold higher for the BFM protocol than MB, whereas costs of cytostatic drugs were comparable in both groups. In Russia both protocols were feasible. During consolidation therapy tolerance to treatment was better in MB 91 compared with BFM 90m, whereas toxicity during induction therapy was similar in both protocols. With respect to costs and side-effects, the MB 91 protocol appears to be an alternative to established protocols for countries with limited financial and clinical resources. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

UNTIL THE late 1980s, treatment results with non-standard treatment strategies of childhood acute lymphoblastic leukaemia (ALL) in the Soviet Union were poor. With the introduction of the German Berlin-Frankfurt-Münster (BFM) protocol in several centres, therapy results were improved considerably. However, Russian physicians had to deal with increasing side-effects requiring more blood product transfusions, frequent use of intravenous (i.v.) antibiotic and antimycotic therapy, use of drug assay monitoring of high-dose therapy, and the overall high costs of the treatment. An unsatisfactory hygienic standard, a poor quality of

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Table 1. *ALL BFM* 90*m, protocol elements I–IV*

Drug	Dosage/m^2	Protocol Ia	Protocol Ib	Protocol M	Protocol II
Prednisone p.o.	60 mg/d	Weeks 1–5			
Dexamethasone p.o.	10 mg/d				Weeks 23–26
Daunorubicin i.v. (1 h)	30 mg/w	Weeks 2–5			
Doxorubicin i.v. (1 h)	30 mg/w				Weeks 24–27
Vincristine i.v.	1.5 mg/w	Weeks 2–5			Weeks 24–27
L-Asparaginase i.v.	10 000 U/3d	Days 12–33			Weeks 24–25§
Cyclophosphamide i.v.	1000 mg/w		Weeks 6,10		Week 28
Cytosine arabinoside i.v.	75 mg/d 4 x/w		Weeks 6–10		Weeks 28–29
6-Mercaptopurine p.o.	60 mg/d		Weeks 6–9		
6-Mercaptopurine p.o.	25 mg/d			Weeks 13–20	
6-Thioguanine p.o.	60 mg/d				Weeks 28–29
Methotrexate i.v. (36 h)*	1000 mg/w			Weeks 14, 16, 18, 20	
Methotrexate i.t.	Age dependent/w†	Weeks 1, 3, 5‡	Weeks 7, 9	Weeks 14, 16, 18, 20	Weeks 28, 29

*Methotrexate infusion followed by a standard scheduled leucovorin rescue †Intrathecal therapy: age <1 year, 6 mg; $\geq 1-<2$ y, 8 mg; $\geq 2-<3$ y, 10 mg; ≥ 3 y: 12 mg. ‡In case of initial CNS involvement two additional doses on weeks 2 and 4 §L-ASP on first and fourth day of each week. p.o., orally; i.t., intrathecal; i.v., intravenous.

blood banks and lack of adequate supportive care including sterile disposable material and advanced generation i.v. antibiotics frequently led to severe and sometimes lethal complications [1, 2]. In 1991, a new protocol for treatment of childhood ALL in Russia was developed as a cooperative project between the Institute of Paediatric Haematology, Moscow and the Department of Paediatric Oncology and Haematology of the Charité-Virchow Medical Centre Berlin. The main aims were to achieve high antileukaemic efficacy by combining effective therapy elements from several successful protocols; to avoid high-dose therapy, to avoid high cumulative doses of anthracyclines and severe myelotoxicity with the resulting need for supportive care; to avoid central nervous system (CNS) irradiation for the majority of the patients; to minimise need for inpatient treatment and reduce costs of the whole treatment. Since 1991, a pilot study was performed at the Republican Children's Hospital Moscow to compare the new protocol, Moscow-Berlin (MB) 91, with the modified ALL BFM 90 protocol [3]. This randomised study has been ongoing since 1993 [4]. Interim results do not show a difference in event-free survival (EFS) for patients treated according to the ALL MB 91 protocol compared with patients treated according to the ALL BFM 90m protocol: EFS was $82 \pm 5\%$ versus $77 \pm 10\%$ for the pilot study cohort after 3 years and $81 \pm 7\%$ versus $78 \pm 10\%$ for the patient cohort of the subsequent randomised study after 3.5 years [3, 4]. Rates of therapy-related deaths and relapses were not different in both groups. In this article toxicity data of the non-randomised single centre study period are presented.

PATIENTS AND METHODS

The protocol ALL BFM 90m

The protocol ALL BFM 90m is a modified version of the original German protocol ALL BFM 90 [5]. It consists of 4 protocol elements, induction (protocol Ia), first consolidation (protocol Ib), second consolidation (protocol M) and reinduction (protocol II). The dose and time schedules are presented in Table 1. Treatment response was evaluated using the peripheral blast count on day 8 and the remission status of the bone marrow on day 33.

In contrast to the original protocol ALL-BFM 90, high-dose methotrexate (HD-MTX) in protocol M (element III) was reduced to a dose of 1 g/m^2 i.v. (intermediate dose: ID-MTX) as a 36-h infusion followed by leucovorin rescue. At the end of protocol II cranial irradiation was administered at an age and risk group dependent dose (Table 2).

Stratification of patients treated according to ALL BFM 90m was identical to the original protocol. According to the original protocol ALL BFM 90 patients with an initial risk factor (IRF $= 0.2 \times \log$ (initial blast cell count/μl + 1) + 0.06 $\times$ liver enlargement (cm) + 0.04 $\times$ spleen enlargement (cm)) exceeding 0.8, patients with T cell phenotype or patients with initial CNS involvement were stratified as an intermediate risk group (MRG).

Maintenance therapy consisted of daily 6-mercaptopurine 50 mg/m^2 orally and weekly MTX 30 mg/m^2 orally at a duration of 18 months. Dosage was adapted to the leucocyte count, keeping it in the range of $2-4 \times 10^9$/l.

The protocol ALL MB 91

The protocol ALL MB 91 consisted of an induction and three consolidation elements. Dose and time schedules are listed in Tables 3 and 4. At the end of consolidation high risk (HR) patients received cranial irradiation at an age-dependent dose (<1 year, no irradiation; 1–2 years: 15 Gy; >2 years: 18 Gy; patients with initial CNS involvement >3 years of age, 24 Gy) [4].

Maintenance therapy consisted of daily 6-mercaptopurine 50 mg/m^2 orally and weekly MTX 30 mg/m^2 intramuscularly (i.m.) interrupted by another 8 vincristine/dexamethasone re-induction pulses similar to those during consolidation therapy at an interval of 6 weeks. Triple intrathecal therapy (TIT) was continued four more times at the start of a re-induction pulse. After cranial irradiation, TIT was given without MTX. After the last re-induction pulse, 6-mercaptopurine/MTX was continued for a total of 18 months.

All patients of the MB 91 group were stratified into the standard risk (SR) group except patients with the following risk criteria: less than 1 year of age, more than 50×10^9/l

Table 2. *ALL BFM* 90*m. Dosage of cranial irradiation*

Age	<1 year	≥ 1 and <2 years	≥ 2 years
Standard/medium risk group	0 Gy	12/18 Gy	12/18 Gy
Initial CNS involvement	0 Gy	18 Gy	24 Gy

Table 3. ALL MB 91, protocol elements I–IV

Drug	Dosage/m²	Induction	Consolidation I	Consolidation II	Consolidation III
Dexamethasone p.o.	6 mg/d	Weeks 1–5	Weeks 14–15	Weeks 22–23	Weeks 30–31
Daunorubicin i.v. (6 h)	45 mg/w	Weeks 2, 4*			
Daunorubicin i.v. (6 h)	30 mg/w		Weeks 8, 11, 14†	Weeks 16, 19†	
Vincristine i.v.	1.5 mg/w	Weeks 2–7	Weeks 14, 15	Weeks 22–23	Weeks 30, 31
L-Asparaginase i.m.	10 000 U/w	Weeks 6, 7	Weeks 8–13	Weeks 16–21	Weeks 24–29
6 Mercaptopurine p.o.	50 mg/d		Weeks 8–13	Weeks 16–21	Weeks 24–29
Methotrexate i.m.	30 mg/w		Weeks 8–13	Weeks 16–21	Weeks 24–29
MTX/ARA-C/DEXA i.t.	Age dependent/w	Weeks 1–5, 7	Week 14	Week 22	Weeks 28, 29

*Daunorubicin on day 4 in high risk patients and in case of >10% lymphoblasts in bone marrow on day 15. †Daunorubicin only in high risk patients. p.o., orally; i.m., intramuscular; i.v., intravenous; i.t., intrathecal.

leucocytes at diagnosis, initial CNS involvement and/or T cell phenotype.

Study design; criteria for inclusion of patients in the analysis

Patients included in the present toxicity analysis were treated during a single-centre study period from June 1991 until August 1994 including the non-randomised patients of the pilot study. Informed consent was obtained from the patients and/or their guardians. Toxicity data were evaluated for the intensive treatment period. Included were all patients with non-B-ALL, less than 16 years of age, treated according to one of the above-mentioned protocols and with complete documentation of the four protocol elements of the intensive treatment period, i.e. protocol Ia, Ib, M and II for ALL BFM 90 m and induction and consolidation I-III for ALL MB 91. All patients for whom documentation of the four protocol elements of the intensive treatment period was incomplete due to the occurrence of an early adverse event ($n=11$) or due to an interruption of the protocol treatment without medical reasons ($n=9$) were equally excluded from the toxicity analysis for both protocols. Also, all patients ($n=3$) meeting the high risk criteria according to ALL BFM 90 ($>1\times10^9$/l lymphoblasts in the blood count on day 8, no complete remission on day 33, translocation t(9,22) resp. BCR-ABL recombination) were excluded from this analysis. They were treated according to the original ALL BFM 90 protocol with intensified HD-polychemotherapy blocks.

Parameters of toxicity and need of supportive care

The following parameters were analysed: administration of red cell transfusions (ml/m²); platelet transfusion (unit/m²); (criteria for the use of erythrocyte and platelet transfusions were applied uniformly to all patients on the study); duration of i.v. combination antibiotic and antimycotic therapy (days), duration of inpatient treatment (days) and duration of treatment delay (difference of the actual treatment duration to the assumed duration according to the protocols) in days. These parameters were extracted from the documentation forms of the patients' histories. Additionally the duration of aplasia defined as less than 0.5×10^9/l granulocytes, maximum of liver enzyme, creatinine and bilirubin serum levels were analysed. Criteria for transfusion of blood products, start of i.v. antibiotic/antimycotic therapy, need of inpatient treatment and treatment delay were identical for both groups.

Other toxicity parameters such as mucositis, nausea and vomiting, vincristine-related neuropathy and L-asparaginase related allergic reactions and alteration of coagulation factors were not included in this analysis. A standardised evaluation of these parameters had not yet been performed at the treating centre.

Statistics

Independence of quantitative variables was tested using the 2-sided U-test according to Mann–Whitney. Significance of a difference was assumed at a probability of an error of $P<0.05$. Independence of qualitative variables were tested according to the Fisher's exact test.

Table 4. ALL MB 91. Age-dependent dose schedule of triple intrathecal therapy (TIT) for standard risk (SR) and high risk (HR) group

Age	<1 year	≥1–<2 years	≥2–<3 years	≥3 years
ARA-C (mg)	–/20	20/30	26/40	30/50
MTX (mg)	–/6	8/8	10/10	12/12
DEXA (mg)	–/2	2/2	2/2	2/2

ARA-C, arabinoside-cytosine; MTX, methotrexate; DEXA, dexamethosone.

RESULTS

The patient groups included in the present analysis are described in Table 5. There was no significant difference in risk factors between the two groups. The different stratification criteria used in the two protocols resulted in 28 (88%) SR patients and 4 (12%) HR patients in the MB group compared with 10 (40%) SRG patients and 15 (60%) MRG patients in the BFM group. Therefore, only 12% of the MB group received cranial irradiation and additional doses of daunorubicin at a cumulative dose of 240 mg/m², whereas all

Table 5. Patient characteristics

	MB	BFM	*P*
Total	32	25	
Boys	18 (56%)	12 (48%)	n.s.
Girls	14 (44%)	13 (52%)	
Median age (range)	6.5 (1–14.6 years)	7.5 (1.2–15.2 years)	n.s.
Median IRF acc. BFM (range)	0.82 (0.2–1.6)	1* (0.1–2.2)	n.s.
Leucocyte count [1/nl]	5.150	6.550	n.s.
T cell ALL	3 (9%)	6 (24%)	n.s.
CNS-ALL	0	2† (8%)	n.s.

*2 missing cases. †1 missing case. Median initial risk factor according to ALL BFM criteria. IRF, initial risk factor; ALL, acute lymphoblastic leukaemia; CNS, central nervous system; n.s., not significant

BFM patients received cranial irradiation and a cumulative anthracycline dose of 240 mg/m^2.

The median erythrocyte transfusion level was significantly ($P = 0.002$) less in the MB patient group with 505 ml/m^2 (0–1848) compared with 1000 ml/m^2 (177–4114) in the BFM patient group. The median erythrocyte transfusion level was comparable during the induction therapy of both protocols, but was considerably less in the MB group during the three subsequent consolidation elements (Figure 1a).

The median platelet transfusion level was not significantly different, with 2.9 units/m^2 (0–44) in the MB Group and 0 units/m^2 (0–58) in the BFM group. In the MB group, 18 patients (56%) received at least one unit of platelets during the intensive treatment period compared with 12 patients (48%) in the BFM group (Figure 1b).

Median duration of aplasia was not significantly different ($P = 0.2$), with 39.5 days (7–119.5) in the BFM group and 68.5 days (6.5–142.5) in the BFM group (Figure 1c).

In case of fever during aplasia, an empirical combination i.v. antibiotic therapy was started with a standard escalation schedule as long as fever and/or aplasia continued. Median duration of i.v. antibiotic therapy was significantly ($P = 0.002$) less in the MB group with 9 days (0–60) compared with 22 days (0–90) in the BFM group. As already shown for other toxicity parameters, the use of i.v. antibiotic therapy was comparable during induction therapy whereas it

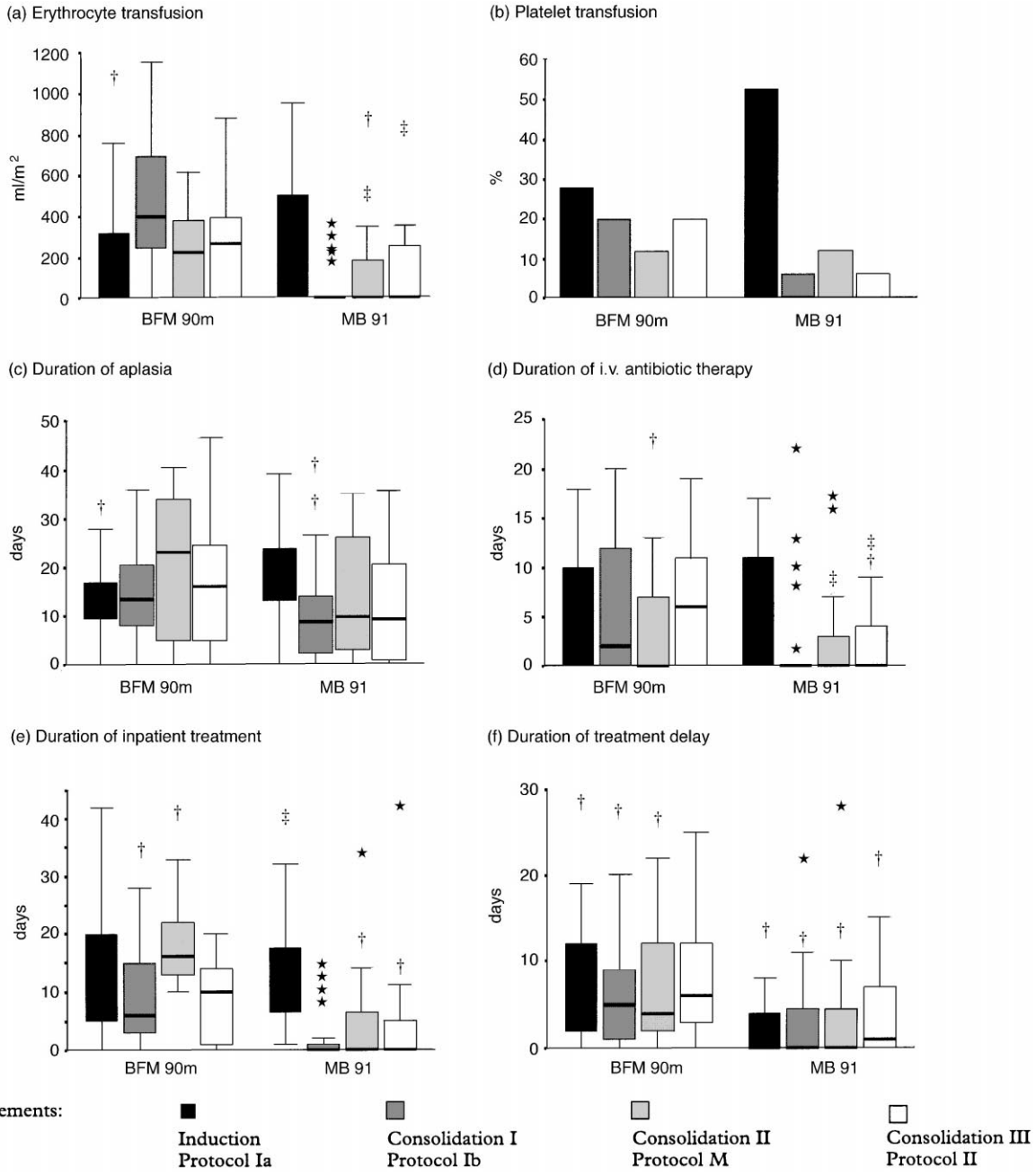

Figure 1. Evaluation of toxicity parameters for the four subsequent protocol elements of the intensive treatment period. (a, c–f) Show median values, quartiles, minimum/maximum, extremes (*>3 interquartile ranges above the quartiles) and outliers (†between 1.5 and 3 interquartile ranges above the quartiles). (b) Shows the percentage of patients receiving at least 1 unit of platelets.

was considerably less during consolidation therapy in the MB group (Figure 1d).

When there was repeated escalation of i.v. antibiotic therapy with persistent fever and typical clinical features suggesting a fungal infection, an i.v. antimycotic agent was added to the antibiotic regimen. Mean duration of i.v. antimycotic therapy was 1.9 days (0–20) in the MB group compared with 4.1 days (0–35) in the BFM group. During intensive treatment, 8 patients (25%) of the MB group received antimycotic therapy compared with 9 patients (36%) in the BFM group. These differences were not significant.

Increase in serum transaminase levels was not significantly different between the two groups. Eighty-seven per cent of MB patients showed alteration of liver enzymes up to WHO toxicity grade III (5-fold above the upper normal level) compared with 76% in the BFM group [6]. Increase in serum creatinine concentrations was also not significantly different between the groups. Twenty-five per cent of MB patients showed serum creatinine levels above the range of WHO toxicity grade I (1.25-fold above the upper normal level) compared with 16% in the BFM group.

Median duration of inpatient treatment was significantly ($P<0.001$) less in the MB group with a median of 17.5 days (5–195) compared with 47 days (15–114) in the BFM group (Figure 1e). Inpatient treatment in the BFM group was comparably high in protocol M (third element) which contains four courses of ID-MTX.

Median duration of treatment delay was significantly ($P<0.001$) less in the MB group with a median of 21 days compared with 39 days in the BFM group (Figure 1f). More than half the MB patients could be treated according to the time schedule of the protocol, whereas half the BFM patients needed a treatment delay of more than 4 days in all protocol elements.

Costs

Costs were calculated on the basis of prices in the German 'Rote Liste' 1995 [7] and prices of a German high standard blood bank. Although the real costs under Russian conditions are much lower, they are very variable and difficult to evaluate. Therefore, comparison of costs of both protocols was considered more important than determining their absolute values.

The costs of cumulative doses of cytostatic drugs amount to 6203 German Marks (DM)/person/m^2 for the intensive treatment period of the MB protocol (+274 DM/person/m^2 for patients of the HR group) compared with 7370 DM/person/m^2 for the BFM protocol. Costs of the maintenance therapy were 7726 DM/person/m^2 for the MB protocol compared with 3560 DM/person/m^2 for the BFM protocol. This was due to the weekly i.m. administration of MTX in the MB maintenance therapy compared with oral MTX administration in the BFM protocol.

Taking into account the mean need of supportive care parameters (i.v. antibiotic and antimycotic therapy according to a standard escalation schedule and transfusion of erythrocytes and platelets) evaluated in this analysis, costs of supportive therapy amounted to 8220 DM/person/m^2 for MB patients compared with 12 040 DM/person/m^2 for BFM patients.

Mean costs/person/m^2 of inpatient treatment were 1.73-fold higher in the BFM group with 52 days compared with 30 days in the MB group.

This calculation did not include the costs of sterile disposable material, infusion solutions, outpatient treatment and travel expenses of the patients and their families.

DISCUSSION

The toxicity and need for supportive care of two protocols for the treatment of childhood ALL in Russia were analysed following a single centre non-randomised study design. The modified ALL BFM 90m protocol had already been in use for 3 years. According to the concept of the original German protocol it appeared that it would be necessary to perform cranial irradiation for all patients, in order to maintain effective antileukaemic CNS protection since with the ALL BFM 90m protocol HD-MTX had to be reduced from 5 g/m^2 given as a 24 h infusion to 1 g/m^2 (ID-MTX) as a 36 h infusion due to lack in the treating centre of reliable MTX serum level monitoring [8].

The main differences of the ALL MB 91 and the ALL BFM 90m protocol are the use of dexamethasone instead of prednisone during induction therapy in the MB protocol, a lower cumulative dose of anthracyclines and avoidance of cranial irradiation for the majority of patients, and avoidance of HD-MTX, ID-cyclophosphamide and cytosine arabinoside pulses. Compared with the ALL BFM 90m protocol, the use of low-dose MTX as well as the use of L-asparaginase, vincristine and intrathecal therapy were intensified.

In several studies the better antileukaemic efficacy of dexamethasone compared with predisone has been shown [9–11]. It can be accounted for by a higher steroid receptor affinity of dexamethosone [12] and the higher serum and cerebro-spinal fluid (CSF) half-life of dexamethasone [13]. Moreover, a better sensitivity of lymphoblasts towards dexamethasone has been demonstrated in *in vitro* resistance assays [14, 15]. The use of dexamethasone in the MB 91 protocol is scheduled similar to the Dutch ALL VI study. However, the ALL VI protocol differs in that it uses three courses of HD-MTX 2 g/m^2 and not intensified weekly L-asparaginase for consolidation of remission. The antileukaemic efficacy of weekly administered L-asparaginase during consolidation therapy was proven by randomised consecutive studies of the Dana-Farber Cancer Institute [16, 17]. Intramuscular administration of L-asparaginase has been shown to be equally effective but less toxic in a randomised analysis of the Children's Cancer Study Group [18].

Antileukaemic CNS protection in the MB protocol is warranted by the intensive use of dexamethasone, a continuous asparagine depletion in the CSF [19], and the extended use of intrathecal triple therapy. Long-term toxicity could be shown to be considerably less for children receiving TIT compared with cranial irradiation [20]. Several studies have shown sufficient neuroprotection with prolonged intrathecal therapy compared with cranial irradiation for the majority of children with ALL [21, 22], except for patients with T cell phenotype or those with initial CNS involvement [23, 24].

The patient characteristics were well balanced between the included MB and BFM patients. However, due to the stratification criteria, only 12% of the MB patients received cranial irradiation and an intensified anthracycline treatment, whereas all BFM patients received cranial irradiation of at least 12 Gy and 8 doses of anthracyclines. This reduction in treatment intensity did not affect the EFS of the MB patients compared with the BFM patients [4].

Toxicity parameters of the present analysis refer mainly to the acute myelosuppressive effect of chemotherapy. With regard to most relevant parameters, the MB 90 protocol induced less myelotoxicity than the ALL BFM 90m protocol.

Whereas this difference was only marginal during induction therapy, it was considerable during consolidation therapy. Toxicity during induction therapy, however, is mainly due to disease-related myelosuppression. Myelosuppression is the main risk factor for severe infections resulting in expensive i.v. combination antibiotic therapy which had to be performed less frequently in the MB patient group.

Since the use of erythrocyte and platelet transfusions was standardised, frequency of transfusion can serve as a valid parameter for indicating suppression of erythro- and thrombopoiesis. The risk of viral infection due to interventional transfusion of blood products has to be considered, especially in Russia.

Approximately half the costs of cytostatics used in the MB protocol were related to L-asparaginase. Recent pharmacological studies suggest the possibility of a dose reduction, because a 7-day asparagine depletion can be achieved by an *Escherichia coli* L-asparaginase dose lowered to 6000 U/m^2 [25]. Other studies suggest the advantage of a recovering asparagine level 6 days after L-asparaginase administration just before the following MTX administration as the efficacy of MTX depends on an active metabolism of the target cell [26]. A modification of L-asparaginase dosage might be the subject of subsequent clinical studies.

Higher costs of the MB maintenance therapy were due to the i.m. administration of weekly MTX. This administration mode has been chosen because of the uncertain compliance of often rural families and the opportunity of regular medical surveillance of the patient in the course of the i.m. administration. In the past irregular medical surveillance of patients during maintenance therapy led to some fatal complications.

Long-term toxicity of both protocols has yet to be evaluated. Higher CNS toxicity due to cranial irradiation and higher cardiotoxicity due to a higher cumulative anthracycline dose in the BFM treated patient group can be assumed [27, 28].

In conclusion it has been shown that both protocols are feasible under conditions of a high standard Russian clinic. Currently, there is no differences between the two groups for remission rate, EFS, relapse rates and fatal toxic events in both protocols. Some of the presupposed advantages of the MB protocol were confirmed, such as lower myelotoxicity leading to a less interventional supportive care, inpatient treatment and consequently lower costs. These data await confirmation in a larger group of patients in a randomised trial. The MB protocol seems to constitute a reasonable basis for further Russian multicentric trials. The objectives of these trials could be a further reduction of intensity and costs and a further adjustment to specific Russian conditions. These are largely due to long distances between the patients homes and the treating centres, limited quality of the blood banks, limited disposal of advanced generation i.v. antibiotics, lack of long-term central venous catheters and the disastrous financial situation of the health sector.

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