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How Much Is Too Much? Folinic Acid Rescue Dose in Children with Acute Lymphoblastic Leukaemia

Joseph D. Borsi, Finn Wesenberg, Tore Stokland and Peter J. Moe

The effect of folinic acid rescue dose on the event-free survival of 71 children with acute lymphoblastic leukaemia was examined in a retrospective clinical study. All patients, diagnosed between 1 January 1980 and 1 January 1989, were treated according to the Norwegian Pilot protocol which included eight courses of high dose (6–8 g/m²/24 h intravenous infusion) methotrexate. Following the infusion, a uniform dose of 75 mg (at 36 h after the beginning of the drug infusion) and 15 mg (at 39–106 h) folinic acid rescue was administered to all patients, at predetermined intervals. The uniformity of the rescue dose resulted in distribution of dosages in the range of 38–140 mg/m² and 7.5–28 mg/m² for the different periods, respectively, when the dose was recalculated on the basis of the body surface area of the individual patients. The event-free survival of children receiving less or more than 15 mg/m² (75 mg/m²) rescue dose was compared. Although no significant difference was found, a tendency was observed for a lower risk of relapse in patients receiving less folinic acid. No major methotrexate-related toxicity was observed in the group of patients receiving the lower dose of rescue. These observations suggest that the reduction of folinic acid rescue dose below the generally accepted 12–15 mg/m² dose may increase the efficacy of high-dose methotrexate therapy while still remaining safe in preventing treatment-related toxicity. Prospective, randomised clinical trials are needed to examine the role of rescue as a determinant of effective exposure to methotrexate in patients receiving high-dose methotrexate treatment.
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INTRODUCTION

DESPITE THE facts that intermediate and high-dose methotrexate/folinic acid rescue (MTX-FA) therapy seems to have an established role in the treatment of a number of malignancies in adults and in children, and pharmacokinetic parameters [systemic clearance, area under the curve (AUC) and steady state levels] determining systemic exposure to methotrexate have been shown to have prognostic importance in children with acute lymphoid leukaemia (ALL) and osteogenic sarcoma [1–3], no clinical data exist to show the role of folinic acid rescue as determinant of the efficacy of treatment with high-dose methotrexate.

In animal models, it has been shown that the effect of methotrexate may be compromised if the dose of folinic acid is excessive [4]. Recently, Browman *et al.* demonstrated the abrogation of both toxicity and antitumour effects of conventional (low-dose) methotrexate by low-dose folinic acid in adult patients in a double blind placebo controlled randomised clinical trial [5]. Here we report the results of a retrospective analysis in children with ALL; we examined whether such relationship between the dose of folinic acid and the effect of treatment could be determined following high-dose methotrexate therapy.

PATIENTS AND METHODS

Between 1 January 1980 and 1 January 1989, 71 patients older than 1 year of age and with non-B acute lymphoblastic leukaemia were treated according to the Norwegian Pilot Protocol in three

Correspondence to J.D. Borsi.
J.D. Borsi is at the Department of Pediatric Oncology, Second Department of Pediatrics, Semmelweis Medical School, Budapest, Hungary; F. Wessenberg is at the Department of Pediatrics, University of Bergen, Bergen; T. Stokland is at the Department of Pediatrics, University of Tromso; and P.J. Moe is at the Department of Pediatrics, University of Trondheim, 7000 Trondheim, Norway.

Table 1. Patients with non-B-cell ALL, treated according to Norwegian Pilot Protocol between 1 January 1980 and 1 January 1989

	All patients	FA dose (mg/m²)		Age 2–10 FA dose (mg/m²)	
		< 15	≥ 15	< 15	≥ 15
Patients	71	21	50	8	45
Boys	40	8	32	1	29
Girls	31	13	18	7	16
Risk					
Standard	25	6	19	5	19
Increased	22	9	13	1	12
High	24	6	18	2	14
Total relapses	21	5	16	1	15
BM	11	4	7	1	6
CNS	1	0	1	0	1
Testis	2	1	1	0	1
Combined	7	0	7	0	7
EFS (S.E.) %	64.8	72.6	61.1	75	58.1
	(6.2)	(9.6)	(7.9)	(21.1)	(8.8)
Ratio O/E relapses		0.75	1.14	0.34	1.17

FA = folinic acid, EFS = event-free survival, O/E = observed/expected.

of five health regions of Norway. The mean age of patients at diagnosis was 5.83 years (median 4.5, range 1–14 years). Between 1 January 1980 and 1 January 1985, only high-risk patients received this therapy; following this date, all patients (standard, increased and high risk) were treated by this protocol. High-risk was defined as white blood cells (WBC) > 50 × 10^9/l, and/or mediastinal mass or CNS disease at diagnosis; and increased risk was defined as WBC 30–50 × 10^9/l, and/or age between 1–2 years or more than 10 years at diagnosis. Table 1 provides the distribution of characteristics (sex, risk, relapses) of patients in this study.

Details on the protocol have been previously published elsewhere [6, 7]. During the consolidation and maintenance phase of the treatment, all patients received eight doses of high-dose (6–8 g/m²) methotrexate as a 24 h continuous intravenous infusion with 3 l/m² hydration and adequate alkalinisation. The folinic acid rescue schedule consisted of a uniform dose of 75 mg folinic acid intravenously at 36 h after the start of the infusion, followed by a uniform dose of 15 mg intravenously in every third hour between hours 39–63, and a uniform dose of 15 mg orally every sixth hour between hours 69–106, or until serum methotrexate levels fell below 5 × 10^{-8} mol/l.

A total of 547 treatments with high-dose MTX-FA rescue were administered to the patients reported here. The median observation time for the patients in this study was 5.63 years (range 1.5–9.9 years).

Body surface area of the patients was calculated on the basis of weight and height, using standard methods. The dose of folinic acid per square metre was determined by division of 75 or 15 by the surface area of the patient at the time of the treatment with methotrexate. Mean of the individual dosages of folinic acid administered during the eight treatment courses per patient was used in the statistical calculations. Standard techniques were applied to construct a life-table estimate of event-free survival [8]. The logrank test [9, 10] was utilised for univariate comparisons of event-free survivals.

RESULTS

The uniform doses of 75 mg and 15 mg of folinic acid resulted in a wide range of actual folinic acid doses/m² delivered to the individual patients. Figure 1 depicts the distribution of doses when recalculated per square metre for the periods of rescue administration when 15 mg folinic acid was given.

The patients were divided into two subgroups, according to the mean dose of folinic acid. Although this gave an obvious loss of statistical power, from the clinical point of view we felt it important to use a cut-off point of folinic acid dose of 15 mg/m², as most intermediate-dose and high-dose methotrexate protocols used in paediatric oncology utilise folinic acid at a dose of 15 mg/m². There were 21 patients who received less than 15 mg/m² folinic acid (Group A) and 50 patients who received a rescue dose to 15 mg/m² or more (Group B). (Patients who received less than 15 mg/m² folinic acid also received less than 75 mg/m² rescue at 36 h after the start of the methotrexate infusion). 16 relapses occurred in Group B and only 5 in Group A. More combined relapses were found in Group B, whereas no isolated CNS relapses were detected in either of the two groups (Table 1).

The event-free survival (EFS) for the two groups is shown in Fig. 2. The EFS for the patients who received less folinic acid was 72.6% vs. 61.1% for the patients to whom a higher dose was given. The difference between the two subgroups was statistically not significant by the logrank test (χ^2, $P > 0.05$). The tendency is similar—higher survival for the patients receiving less than 15 mg/m² folinic acid rescue—but the differences were not statistically significant ($P > 0.05$) whatever characteristics (sex, risk group) were used to further group the patients (Table 2). However, for girls, receiving less than 15 mg/m² folinic acid was associated with a more than 2-fold lower risk for relapse of the disease. Also, none of the 6 standard-risk patients, who received less than 15 mg/m² rescue, relapsed, in contrast to the 4 relapses of 19 standard risk cases, who received higher rescue dose.

When only those patients were considered who were 2–10 years old at the time of diagnosis, 1 relapse occurred in the group of 8 children who received less than 15 mg/m² folinic

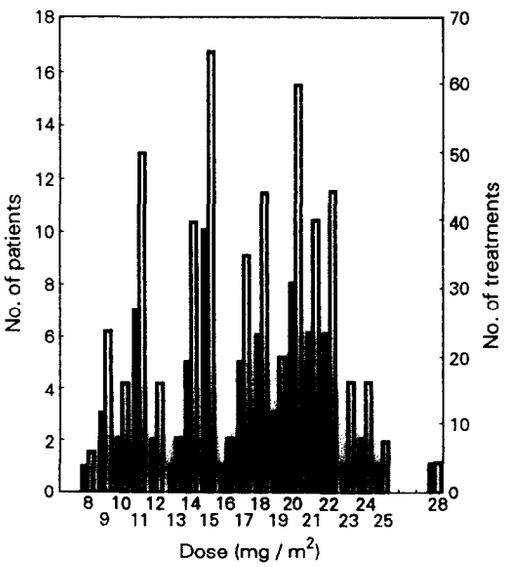

Fig. 1. Frequency distribution of folinic acid dosages and treatments. ■ = Patients, □ = treatments.

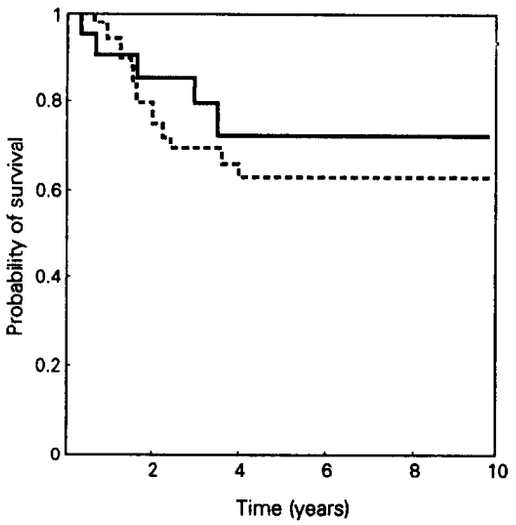

Fig. 2. Event-free survival of patients with different dosages of rescue. —— = <15 mg/m², ---- = >15 mg/m².

acid, and 15 relapsed of the 45 patients who received more than that dose, resulting in a 3.5-fold higher risk for relapse ($P = 0.1$) (Table 1).

DISCUSSION

Results of studies in experimental systems suggest that the effect of methotrexate is determined by a balance of exposure to methotrexate and folinic acid. Our study is the first clinical report to demonstrate that the dose of folinic acid rescue may influence the survival of patients treated with high-dose methotrexate.

Table 2. Event-free survival and relative risk for relapse in different subgroups of patients

	n	Probability of EFS (S.E.)	O/E relapses	Relative risk of relapse	*P**
Boys					
< 15 mg/m²†	8	0.58 (0.18)	0.90	1	
					>0.05
⩾ 15 mg/m²	32	0.52 (0.10)	1.33	1.5	
Girls					
< 15 mg/m²	13	0.81 (0.09)	0.6	1	
					>0.05
⩾ 15 mg/m²	18	0.69 (0.11)	1.66	2.76	
Risk					
Standard					
< 15 mg/m²	6	1.0 (0.0)	0.0	0	
					0.1
⩾ 15 mg/m²	19	0.75 (0.11)	1.4	1.4	
Increased					
< 15 mg/m²	9	0.63 (0.18)	0.93	1	
					>0.05
⩾ 15 mg/m²	13	0.59 (0.16)	1.1	1.2	
High					
< 15 mg/m²	6	0.67 (0.19)	0.68	1	
					>0.05
⩾ 15 mg/m²	18	0.54 (0.11)	1.12	1.66	

* Logrank test.
† Folinic acid dose.

Leukaemic patients older than 10 years of age are usually considered as being at a higher risk for relapse of the disease [11]. On the basis of the dose of folinic acid, we have identified a small subgroup of patients, who, in spite of their older age (8–14 years), had better survival than the rest of the patient group. When patients older than 10 years of age at diagnosis were excluded from the comparison, an even greater difference was noted in favour of those patients who received less rescue. However, the differences observed in this study were not statistically significant, perhaps due to the small number of cases.

There was no major clinical toxicity related to methotrexate in the group of patients receiving less than 15 mg/m² rescue. However, experience with these 21 patients shows that receiving folinic acid in a dose range of 7.5–14.9 mg/m² is certainly not enough to recommend the administration of e.g. 7.5 mg/m² rescue following high-dose methodtrexate as standard. Nevertheless, it can be clearly concluded that doses of folinic acid lower than the usually applied "magic" 12–15 mg/m² may safely protect from toxicity related to methotrexate, with a possible benefit of increasing therapeutic efficacy.

The pharmacokinetics of methotrexate was not studied systematically in these patients. Our previous observations indicate that the pharmacokinetics of methotrexate is age-dependent [12], younger patients having lower steady state methotrexate levels and thus lower systemic exposure to methotrexate. It is possible that superior survival in the older patients presented here reflects to a combined effect of lower rescue dose and higher systemic exposure to the antifolate.

There are a number of limitations (retrospective analysis, small sample size, lack of chromosomal and immunological work-up and lack of multivariate analysis) in our investigation. This paper, however, covers all patients in three of five health regions in Norway for a 9-year period. It is not possible to add more patients to this study, as the protocol was changed since the above observations were made. However, the results presented here together with those of Browman *et al.* [5] can serve as a basis for controlled clinical trials focusing on the subject of folinic acid dose when high-dose methotrexate therapy is administered.

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Malignant Melanoma and Renal Cell Carcinoma: Immunological and Haematological Effects of Recombinant Human Interleukin-2

Khizar Hayat, Sheila Rodgers, Lesley Bruce, Robert C. Rees, Karen Chapman, Steve Reeder, Mark S. Dorreen, Eamonn Sheridan, Thiagarajan Sreenivasan and Barry W. Hancock

The immunological and haematological effects of continuous infusion of recombinant human interleukin-2 (rhIL-2) in 6 patients with metastatic melanoma and 6 with disseminated renal cell carcinoma are reported. In patients with malignant melanoma dacarbazine was given before IL-2; in renal cell carcinoma IL-2 alone was given. In malignant melanoma, 1 complete (CR) and 1 partial response (PR) were seen; 2 patients had stable disease (SD) and 2 progressive disease (PD). In renal cell carcinoma 4 patients had SD and 2 PD. Toxicity of IL-2 therapy was minimal. All patients showed increased cytotoxicity, that was not major histocompatibility complex restricted, towards target cells sensitive and insensitive to natural killer cells. These activities varied between individual patients and were less marked in cases of renal cell carcinoma. Cellular proliferative responses increased in all patients, being consistently higher following the first course of therapy, as did HLA-DR, CD16 and CD25 activation marker expression. Hypersegmentation of neutrophils and eosinophilia were commonly observed, and in renal cell carcinoma these changes were accompanied by abnormal lymphocyte morphology.
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INTRODUCTION

OVER THE past 5–10 years, clinical trials with recombinant human interleukin-2 (rhIL-2) have confirmed its antitumour activity in various types of malignancy, particularly malignant melanoma and renal cell carcinoma [1]. The role of IL-2 as an antitumour therapeutic agent was established in preclinical studies where regression of primary tumours and secondary metastases were observed following therapy [2, 3]. The first results from clinical trials of recombinant IL-2 in various types of cancer were published by Rosenberg's group [4] where favourable response rates in malignant melanoma and renal cell cancer were seen (20–25% partial and complete responses [PR and CR]) but at the cost of severe toxicity (e.g. hypotension, fluid retention and life-threatening pulmonary oedema). In these initial clinical trials, the IL-2 was administered in high, 8-hourly, bolus injections. The widely fluctuating serum levels of the cytokine with transient high peak exposures may have contributed to the severe toxicity. In preclinical studies the half-life of rhIL-2 is less than 1 hour [5], suggesting that if IL-2 were given by continuous infusion, antitumour response could be maintained but with less toxicity [6]; this has been confirmed by West *et al.* [6].

Dacarbazine is considered to be the most active cytotoxic agent in patients with metastatic melanoma with response rates varying between 15 and 20% [7]. Thus, it has been suggested that combining this chemotherapeutic agent with IL-2 might provide a significant benefit over single agent administration [8].

Correspondence to K. Hayat.
K. Hayat, S. Rodgers, L. Bruce, K. Chapman, M.S. Dorreen, E. Sheridan, T. Sreenivasan and B.W. Hancock are at the Department of Clinical Oncology, Weston Park Hospital, Sheffield S10 2SJ; and R.C. Rees, K. Chapman and S. Reeder are at the Department of Experimental and Clinical Microbiology, Section of Tumour Biology and Immunology, University of Sheffield Medical School, Sheffield, U.K.
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