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[Article]

Impact of Morning Versus Evening Schedule for Oral Methotrexate and 6-Mercaptopurine on Relapse Risk for Children with Acute Lymphoblastic Leukemia

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Abstract

Purpose: To study the risk of non-B-cell acute lymphoblastic leukemia (ALL) relapse in relation to the routines of administration of oral methotrexate (MTX) and 6-mercaptopurine (6MP) and to the erythrocyte (E) levels of the intracellular cytotoxic metabolites, that is, MTX polyglutamates and 6-thioguanine nucleotides (E-MTX and E-6TGN).

Patients and Methods: E-MTX and E-6TGN levels were measured at least three times (medians, eight and nine) in 294 children with non-B-cell ALL during oral MTX and 6MP therapy. For each patient, we registered (a) the individual circadian schedule of drug administration and (b) the coadministration of food, and (c) calculated a mean (m) of all E-MTX and E-6TGN measurements and (d) the product of mE-MTX and mE-6TGN (mE-MTX * 6TGN), due to their synergistic action.

Results: A total of 42 patients were on a morning schedule, 219 were on an evening schedule, and 33 had miscellaneous routines. A total of 149 patients took the drugs with meals, 106 took the drugs between meals, and 39 had varying routines. With a median follow-up of 78 months, ALL has recurred in 66 patients. The patients on an evening schedule had a superior outcome [probability of event-free survival (pEFS) = 0.82 ± 0.03 vs. 0.57 ± 0.08; p = 0.0002], whereas the coadministration of food did not significantly influence outcome. Patients with a mE-MTX * 6TGN < 813 [product of median mE-MTX (4.7 nmol/mmol Hb) and mE-6TGN (173 nmol/mmol Hb)] had an inferior outcome (pEFS = 0.70 ± 0.04 vs. 0.85 ± 0.03; p = 0.003), even if only patients on an evening schedule were analyzed. Thus, 109 patients on the MTX/6MP evening schedule with an mE-MTX * 6TGN <= 813 $(nmol/mmol\ Hb)^2$ had a pEFS of 0.89 ± 0.03 and a probability of continuous hematopoietic remission of 0.91 ± 0.03.

Conclusions: An evening schedule should be recommended for oral MTX/6MP maintenance therapy. The value of individual dose adjustments by E-MTX and E-6TGN remains to be determined in prospective randomized trials.

The probability of event-free survival (pEFS) for childhood acute lymphoblastic leukemia (ALL) has improved to 70-75% with modern intensive multidrug combination chemotherapy (1,2). Although an impressive achievement, 50% of these patients are at an unnecessary risk of serious late effects (that is, the patients who were likely to be cured by the less toxic regimens applied in the 1970s and early 1980s) (1,3,4). These protocols include vincristine and steroids for induction therapy and high-dose intravenous methotrexate (MTX) and oral MTX and 6-mercaptopurine (6MP) for consolidation and maintenance therapy. If such protocols are to be reintroduced to good-prognosis patients [for example, defined by DNA index (5), by in vitro drug sensitivity profiles (6), or by early detection of minimal residual disease (7)], new guidelines for schedule and dose adjustments strategies are needed to optimize oral MTX and 6MP therapy. In 1985, Rivard et al. (8) published data that indicated a morning dosage of oral MTX/6MP is associated with inferior outcome compared with an evening schedule. To explore these circadian data further, the Nordic Society for Pediatric Hematology and Oncology in 1988 initiated the NOPHO ALL-88 study to determine the clinical significance of (a) morning versus evening MTX/6MP administration, (b) coadministration of food, and (c) MTX/6MP pharmacokinetics as reflected by the erythrocyte concentrations of the cytotoxic metabolites of MTX and 6MP (9,10). The major cytotoxic metabolites of MTX and 6MP are the MTX polyglutamates and 6-thioguanine (6TGN) nucleotides, respectively (11,12). During MTX/6MP therapy, these metabolites accumulate intracellularly, including in erythrocytes (E-MTX and E-6TGN), and both E-MTX and E-6TGN are correlated with the degree of myelotoxicity and with remission duration (13-16).

PATIENTS AND METHODS

Patients

Patients included in the NOPHO ALL-88 study (a) were diagnosed with non-B-cell ALL between July 1986 (when a new common set of protocols was introduced for Denmark, Finland, Iceland, Norway, and Sweden) and December 1990 (the end of accrual), (b) were >= 1 year and < 15 years of age at diagnosis, (c) were in first remission after induction and consolidation therapy and on oral weekly MTX and daily 6MP maintenance therapy when entering the study, (d) had at least three measurements of both E-MTX and E-6TGN, and (e) had their circadian schedule of

MTX/6MP administration registered. A total of 294 patients fulfilled these criteria. Participation in the study was optional, and the patients who entered the study did not differ significantly from those not included in respect to the distribution of risk factors or outcome (16). Three patients were excluded because of a lack of data on their circadian drug administration. The material included 130 girls and 164 boys with 122 cases of standard-risk (SR), 121 cases of intermediate-risk (IR), and 51 cases of high-risk (HR) ALL. Risk classification was determined by white blood cell count (WBC), age (SR, 2-10 years and WBC < 10×10^9/L; IR, <2 years or >= 10 years and/or WBC 10-49 × 10^9/L; and HR, WBC >=50 × 10^9/L), and the presence of central nervous system or testicular leukemia, a mediastinal mass, T-cell disease, or certain cytogenetic translocations (all HR criteria). At the time of diagnosis, the median age of the patients was 4.2 years (range, 1.0-14.9). No patients in first remission received a bone marrow transplantation, developed a secondary malignant neoplasm, died, or were lost for follow-up. The patients who stayed in first remission had a median length of follow-up from achieved remission to the end of follow-up (December 31, 1994) of 78 months (range, 48-100 months).

Therapy

Induction and consolidation therapy were risk group adapted. The NOPHO ALL-SR induction protocol consisted of vincristine (2.0 mg/m^2 weekly × 6), prednisone (60 mg/m^2/day for 5 weeks and then tapering), doxorubicin (40 mg/m^2 on days 1, 22, and 36), asparaginase (10,000 IU/m^2 on days 37-46), and intrathecal MTX therapy (days 1, 8, 15, and 29; <3 years, 10 mg, and >=3 years, 12 mg); NOPHO ALL-SR consolidation therapy consisted of high-dose MTX (1.0 g/m^2/24 h for three times with intrathecal MTX therapy and leucovorin rescue). In addition, patients with SR-ALL received during the first year of maintenance therapy at 4-week intervals alternately either high-dose MTX or vincristine (2.0 mg/m^2 × 1)/prednisone (60 mg/m^2 for 1 week) reinductions until five of each had been given. The NOPHO ALL-IR and ALL-HR protocols were based on the ALL-BFM-83 therapy program modified in two respects. The duration of therapy was 2 years from achieved remission for all patients, and cranial irradiation was reduced for children <2 years of age at the time of irradiation (IR, <2 years 15 Gy vs. 18 Gy if >=2 years; and HR, <2 years 20 Gy vs. 24 Gy if >=2 years).

The maintenance therapy doses of oral MTX and oral 6MP started at 20 mg/m^2/week and 50-75 mg/m^2/day, respectively. The blood counts and doses of MTX and 6MP were not registered centrally, but the doses of MTX and 6MP were to be adjusted to a target WBC of 1.5-3.5 × 10^9/L for all patients. During maintenance therapy, blood counts were performed at least monthly.

Circadian Time Schedule of MTX/6MP and Coadministration of Food

The therapy protocol included no recommendation as to coadministration of food and at what time of the day to take MTX and 6MP. During maintenance therapy when the patients were in first remission, parents were questioned on what time of the day their child routinely took MTX and 6MP. This information was obtained for 278 of the 294 patients. For the remaining 16 patients, 15 of whom were in first remission by December 31, 1994, information regarding the time of medication was obtained through retrospective interviews. During maintenance therapy, the parents of 273 of the 294 children provided information on whether their child routinely took MTX and 6MP together with a meal. Because of expected recall bias, the remaining 21 families were not interviewed at the end of follow-up. Patients who did not have a consistent routine in respect to morning versus evening schedule or the coadministration of food were classified as miscellaneous (Table 1).

	Time schedule			
	Morning	Evening	Other*	Total
Administration of MTX/6MP with a meal				
Yes	33	98	18	149
No	7	94	5	106
Other*	2	27	10	39
Total	42	219	33	294
Patient features				
Gender (male/female)	28/14	114/105	22/11	164/130
Median age (years)	3.5	4.3	4.3	4.2
Median white cell count (×10⁹/L)	8	9	5	8
Standard/intermediate/high risk	16/20/6	85/94/40	21/7/5	122/121/51
Relapse: bone marrow/extramedullary	14/4	28/14	7/1	47/19

*Different routines for MTX and 6MP administration, no consistent routine, or lack of data.

TABLE 1. *Time schedule for methotrexate (MTX)/6-mercaptopurine (6MP) medication and its coadministration with food*

E-MTX/E-6TGN

Blood samples for E-MTX and E-6TGN measurements were routinely sent for analyses at a single center. E-MTX was measured at least 48 h after the last dose of MTX. The median numbers of E-MTX and E-6TGN measurements were 8 (range, 3-35) and 9 (range, 3-75), respectively. Of the 294 patients, 90% had E-MTX/6TGN measured at least every other month from the time of study entry until ALL relapse or end of therapy, whichever came first. E-MTX and E-6TGN were measured with a radiochemical ligand assay and a mercury-extraction high-performance liquid chromatographic assay, respectively, as previously described (17,18). Both E-MTX and E-6TGN levels were expressed in nmol/mmol hemoglobin (Hb). For each patient, an arithmetic mean of all measurements was calculated (mE-MTX and mE-6TGN). Since both in vitro and in vivo studies have indicated that MTX and 6MP have synergistic action, the product of mE-MTX and mE-6TGN was calculated for each patient (mE-MTX * 6TGN) (15,16,19). Calculation of mE-MTX * 6TGN either as the product of mE-MTX and mE-6TGN or as the average of the product of E-MTX and E-6TGN for each of a patient's samples gave very similar results [correlation coefficient (r_s) = 0.98].

Statistics

The Mann-Whitney *U* test, Kruskal-Wallis test, and Spearman rank-order correlation analyses were applied to compare distribution of parameters between subgroups and correlation between parameters (r_s) (20). Stepwise Cox multivariate proportional hazards regression analyses were done to detect prognostic factors (21). Parameters were included and excluded from the models at significance limits of 0.05 and 0.10. The Kaplan-Meier method was applied for calculation of remission duration and generation of survival curves (22). Subgroups were compared with the log-rank test (23). Two-sided *p* values of <0.05 were regarded as being significant. Data were analyzed with the SPSS statistical software (24). Cases referred to as extramedullary relapses are all isolated relapses, and patients were censored at the time of this event in analyses of hematopoietic remission (25).

RESULTS

Circadian Time Schedule of MTX/6MP and Coadministration with Food

Of the 294 patients, 42 consistently took MTX and 6MP in the morning (before 10 a.m.), 219 took both drugs in the evening (after 5 p.m.), and 33 had miscellaneous patterns [that is, MTX and 6MP at different hours (n = 24), both drugs at midday (n = 5), or no consistent routine (n = 4)]. A total of 149 patients reported that they routinely took both MTX and 6MP together with a meal, whereas 106 took MTX and 6MP between meals. For 39 patients, such data were not registered (n = 21) or they had miscellaneous routines (n = 18). More boys than girls were on a morning schedule (19.7% vs. 11.7%), but the difference was not significant. Morning versus evening schedule was significantly correlated with whether the patients took their MTX and 6MP with a meal (Table 1) (p = 0.0002). Thus, most patients who took MTX and 6MP in the morning took the drugs with a meal. In contrast, only half the patients who took MTX and 6MP in the evening took the drugs with a meal (Table 1). Patients who took their MTX and 6MP in the morning, in the evening, and with or without a meal did not differ significantly in respect to gender, age, WBC at diagnosis, or risk group (Tables 1 and 2).

	No. of patients	mE-MTX[a]	mE-6TGN[a]	mE-MTX * 6TGN[a,c]	pEFS[d]
Total	294	4.7	173	791	0.77
Gender					
Boys	164	4.9	176	849	0.76
Girls	130	4.2	172	716	0.79
Age (years)					
>5	171	4.7	164	746	0.81
6–9	83	4.6	195	877	0.76
10–14	40	5.0	183	835	0.68
Risk group					
Standard	122	4.7	176	836	0.79
Intermediate	121	4.6	167	757	0.78
High	51	4.2	180	765	0.73
Time schedule					
Morning	42	5.3	165	793	0.57
Evening	219	4.6	176	806	0.82
Other[b]	33	4.4	162	702	0.76
Coadministration with a meal					
Yes	149	4.8	168	744	0.76
No	106	4.9	185	880	0.81
Other[b]	39	4.4	170	722	0.74

[a]Median value for each subgroup. An average erythrocyte methotrexate or 6-thioguanine nucleotide level (nmol/mmol Hb) was calculated for each patient (mE-MTX and mE-6TGN).
[b]Different routines for MTX and 6MP administration, no consistent routine, or lack of data.
[c]Since the distributions of mE-MTX and mE-6TGN are skewed toward lower values, the mE-MTX * 6TGN may for each subgroup be lower than the product of mE-MTX and mE-6TGN for that subgroup.
[d]The 5-year probability of event-free survival.

TABLE 2. *Distribution of mean erythrocyte (mE) methotrexate (MTX), mE 6-thioguanine (6TGN), and mE-MTX * 6TGNa*

mE-MTX/mE-6TGN

For patients staying in remission, the medians of mE-MTX and mE-6TGN were 4.7 nmol/mmol Hb (range, 0.4-10.3) and 173 nmol/mmol Hb (range, 58-871). mE-MTX and mE-6TGN were not related (r_s = 0.01). mE-MTX and mE-6TGN were correlated neither with age, risk group, year of diagnosis, the number of E-MTX or E-6TGN samples, nor with the sampling frequency (Table 2). Boys had higher mE-MTX (p = 0.0008) and mE-MTX * 6TGN (p = 0.001) than did girls, whereas there was no significant difference in their mE-6TGN (Table 2). mE-MTX, mE-6TGN, and mE-MTX * 6TGN did not differ significantly between patients who took MTX and 6MP in the morning, in the evening, and with or without food (Table 2), which indicates that the schedule of MTX/6MP administration did not significantly influence pharmacokinetics or compliance.

Clinical Outcome

A total of 27 girls and 39 boys relapsed (47 in bone marrow), 13-58 (median, 32) months from achieved remission. The overall 5-year probability of continuous hematopoietic remission and of EFS was 0.83 ± 0.02 and 0.77 ± 0.02, respectively. Neither country, gender (male vs. female: 5-year pEFS = 0.76 vs. 0.79), year of diagnosis, WBC at diagnosis, risk group (SR vs. IR vs. HR: 5-year pEFS = 0.79 vs. 0.78 vs. 0.73), mE-MTX, mE-6TGN (continuous variables), nor the number or frequency of E-MTX or E-6TGN measurements were related to the risk of relapse in univariate Cox analyses. In addition, no subgroups of patients defined by mE-MTX or by mE-6TGN (for example, greater or less than the median value or with very high or very low levels of mE-MTX or of mE-6TGN) could be identified to have a clinical outcome that differed significantly from that of the remaining patients. As previously reported, patients with an mE-MTX * 6TGN < 813 (nmol/mmol Hb)^2 (=4.7 * 173; that is, the product of the median values for patients in remission) had a significantly increased risk of relapse (pEFS = 0.70 ± 0.04 vs. 0.85 ± 0.03; p = 0.003) (16).

The outcome for the 42 patients who took their MTX and 6MP in the morning was significantly poorer than for the 219 patients on an evening schedule (pEFS = 0.57 ± 0.08 vs. 0.82 ± 0.03; p = 0.0002). The 33 patients on miscellaneous time schedules had an intermediate outcome (pEFS = 0.76 ± 0.07). For the 219 patients taking their MTX and 6MP in the evening, mE-MTX * 6TGN retained its prognostic significance, whereas this was not the case for

patients on a morning schedule (Fig. 1). Thus, the 109 patients with a mE-MTX * 6TGN >= 813 (nmol/mmol Hb)^2 on the MTX/6MP evening schedule had a pEFS of 0.89 ± 0.03 and a probability of continuous hematopoietic remission of 0.91 ± 0.03. The percentage of patients on an evening schedule increased during the study period. Thus, 67% took the drugs in the evening in 1986-1987, 74% in 1988, and 80% in 1989-1990. However, the favorable outcome for patients taking MTX and 6MP in the evening could not be explained by a generally poorer outcome for patients diagnosed during the early part of the study period. Thus, the 101 patients diagnosed in 1986-1987 had an outcome similar to the 193 patients diagnosed in 1988-1990 (pEFS = 0.79 vs. 0.76).

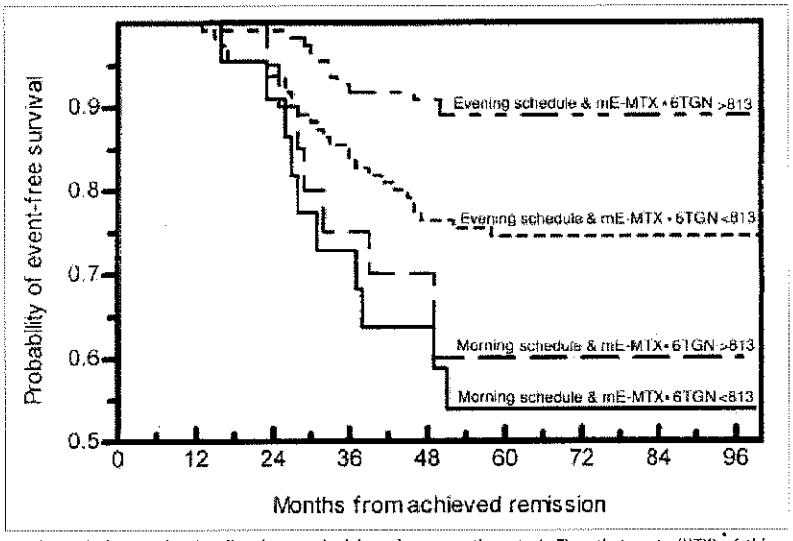

FIG 1. Survival curves by circadian dosage schedule and mean erythrocyte (mE) methotrexate (MTX) * 6-thioguanine (6TGN): evening schedule and mE-MTX * 6TGN >= 813 (n = 109); evening schedule and mE-MTX * 6TGN < 813 (n = 110); morning schedule and mE-MTX * 6TGN >= 813 (n = 20); morning schedule and mE-MTX * 6TGN < 813 (nmol/mmol)^2 (n = 22).

The outcome for the 149 patients who were registered to take their MTX/6MP together with a meal did not differ significantly from the outcome for the 106 patients who took their MTX/6MP between meals (pEFS, 0.76 ± 0.04 vs. 0.81 ± 0.04; p = 0.29). Similarly, patients who took MTX and 6MP with or between meals did not differ in outcome when analyzed within subgroups defined by whether they had mE-MTX * 6TGN < 813 or >= 813 (nmol/mmol Hb)^2, respectively, or whether they were on an evening or a morning MTX/6MP schedule. Thus, if only the patients who took MTX and 6MP with a meal were included, the 33 patients on the morning schedule still had an increased risk of relapse compared with the 98 patients on the evening schedule (pEFS = 0.57 ± 0.09 vs. 0.83 ± 0.04; p = 0.002). In contrast, if only patients on an evening schedule were included, the 98 patients who took their MTX and 6MP with a meal had an outcome similar to the 94 patients who took their drug between meals (pEFS = 0.83 ± 0.04 vs. 0.83 ± 0.04; p = 0.92).

The best-fit model to predict any relapse among the 261 patients who took both MTX and 6MP either in the morning or in the evening included in the final model in the following order of statistical significance: circadian timed dosing (morning = 1, evening = 2, miscellaneous schedules excluded), and mE-MTX * 6TGN [>=813 vs. <813 (nmol/mmol Hb)^2; global p < 0.0001]. The best-fit model to predict hematopoietic relapse included only morning versus evening schedule (global p = 0.0001). Extramedullary relapses were best predicted by a model including only mE-MTX * 6TGN (global p = 0.006). Other parameters tested in the Cox analyses were year of diagnosis; gender, age, and WBC at diagnosis; risk group; mE-MTX (>=4.7 vs. <4.7 nmol/mmol Hb); mE-6TGN (>=173 vs. <173 nmol/mmol Hb); the total number of E-MTX/6TGN measurements; the frequency of measurements; and whether MTX and 6MP were taken with or without a meal.

DISCUSSION

Although, MTX and 6MP are among the most effective agents in ALL chemotherapy (26,27), no consensus on route of administration, schedule, and guidelines for dose adjustments exists (28). Therapeutic drug monitoring to optimize anticancer therapy has been in focus for many years (29). Many studies have suggested that measurements of E-MTX and E-6TGN offer several clinical advantages in this respect. These pharmacokinetic parameters relate to drug doses, bone marrow drug exposure, and metabolic phenotype, and they demonstrate little intraindividual coefficient of variation ([almost equal to]0.10) at an unchanged dose (10,30-33). In addition, they relate significantly both to the degree of myelotoxicity and to the duration of remission (9,13-16,32-35).

The circadian schedule has for a number of drugs been shown to influence significantly the efficacy and toxicity of therapy (36-39). Such a relationship for oral 6MP/MTX maintenance therapy has now been demonstrated by the present study and by the study by Rivard and co-workers (8,40). The reason for the inferior outcome for patients on a morning schedule is unclear. Diurnal differences in MTX and 6MP plasma pharmacokinetics have been suggested to explain the differences in outcome (41-43). However, the interpretation of circadian 6MP pharmacokinetic data is hampered by the large intraindividual variations in 6MP disposition, and others have failed to demonstrate significant diurnal differences (44-46). In addition, the present study demonstrated no significant differences in mE-MTX and mE-6TGN in relation to the circadian time schedule, and mE-MTX * 6TGN retained its prognostic significance in combined analyses with circadian schedule, although only for patients who took MTX and 6MP in the evening. This does of course not rule out that the circadian schedule may relate to other pharmacokinetic parameters. Thus, different MTX polyglutamates rather than the total MTX pool, or the total intracellular 6MP metabolite concentration

(methylated and nonmethylated derivatives) rather than just the 6TGN, should be analyzed in this respect as well as for their relation to clinical outcome (11,34,47). However, these parameters were not included in the present study. Alternate explanations for the poor outcome for patients on a morning schedule could be clinically significant interaction between MTX/6MP and some endogenous substance(s) such as hematopoietic growth factors. Along this line, low bone marrow proliferative activity and low granulocyte-macrophage colony-stimulating factor levels have been demonstrated at night (48-51). In contrast, lymphoblasts probably have their peak activity at night (49,52). Thus, the therapeutic index for MTX/6MP therapy should be highest with an evening dosage. Such a correlation between the time of drug administration and the degree of subsequent toxicity has been demonstrated for other anticancer agents (36,38). If this is the case for MTX/6MP maintenance therapy, patients on an evening dosage would have less myelotoxicity and/or receive higher doses of MTX and 6MP with equal toxicity levels compared with patients on a morning schedule. Such data have not yet been reported, but are explored in the ongoing NOPHO ALL-92 study (16). Even though the reason for the better prognosis for patients taking MTX and 6MP in the evening remains to be determined, it should be recommended that all patients on oral MTX and 6MP are switched to evening MTX/6MP administration, since both this and the study by the Toronto group (8), including in total >400 patients, have reported an advantage of an evening schedule.

The dietary intakes and patterns vary considerably among patients, and this may significantly influence the bioavailability of drugs (53). Reduced bioavailability (or even unmeasurable concentrations) has been demonstrated for both MTX and 6MP when the drugs were administered together with food, and it has been recommended that MTX and 6MP should be taken after an overnight fast (54-57). The clinical importance of these findings, though, is uncertain: (a) the number of patients has been <20 in these studies, (b) others have failed to confirm the data or found that fasting promotes bioavailability of 6MP only for patients who take >70 mg/m^2/day (58,59), (c) titrating the dose of MTX and 6MP by the presence of toxicity should compensate for possible low bioavailability, (d) restricting the individual mode of drug administration could increase noncompliance, (e) we found no significant relation between coadministration of food with MTX and 6MP dosage and mE-MTX or mE-6TGN, and finally (f) the present study demonstrated no significant difference in outcome depending on whether MTX and 6MP were given together with a meal, this being the case also within subgroups defined by whether they took MTX/6MP in the morning or in the evening. This of course does not totally exclude food as an important confounding factor, since the drinking and eating habits were not registered at regular intervals during maintenance therapy, and these habits will vary considerably more than the time schedule for medication, which could well have disturbed reliable analyses of the influence of food.

In conclusion, this study indicates that shifting patients to an evening medication could reduce the risk of treatment failure significantly. In addition, monitoring E-MTX/E-6TGN during maintenance therapy may define a subgroup of patients with reduced relapse rate irrespective of other known risk factors. In the future, optimizing oral MTX/6MP therapy through pharmacokinetically guided dose adjustments might reduce the need for very intensive induction and consolidation therapy for a substantial number of patients and thus reduce the risk of late effects for children with ALL.

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APPENDIX 1. PARTICIPATING PEDIATRIC DEPARTMENTS (ALPHABETICAL ORDER, COUNTRY, AND CITY)

Denmark Schmiegelow K, Rigshospitalet, Copenhagen; Peitersen B, University Hospital, Hvidovre; Jacobsen BB, University Hospital, Odense; Østergård E, University Hospital, Ålborg; and Schrøder H, University Hospital, Århus.

Finland Siimes M, University Hospital, Helsinki; Perkkiö M, University Hospital, Kuopio; Lanning M, University Hospital, Oulu; Mäkipernaa A, University Hospital, Tampere; and Salmi T, University Hospital, Turku.

Iceland Kristinsson J, Landspitalinn, Reykjavik.

Norway Danielsen O, Municipal Hospital, Arendal; Wesenberg F, University Hospital, Bergen; Nielsen B, Municipal Hospital, Bodö, Stensvold K, Municipal Hospital, Drammen; Lund JH, Municipal Hospital Frederiksstad; Danielsen K, Municipal Hospital, Kristiansand; Glomstein A, Rikshospitalet, Oslo; Hellebostad M, Ullevål Sykehus, Oslo; Zanussi G, Municipal Hospital, Stavanger; Stokland T, University Hospital, Tromsø; Moe PJ, University Hospital, Trondheim; Halvorsen B, Municipal Hospital, Tønsberg; and Spangen S, Municipal Hospital, Ålesund.

Sweden Carlsson G, Boden Hospital, Boden; Lindh A, Borås Hospital, Borås; Lundmark KM, Eskilstuna Hospital, Eskilstuna; Fröstad B, Falun Hospital, Falun; Dimberg A, Gällivare Hospital, Gällivare; Adran B-A, Gävle Hospital, Gävle; Mellander L, Eastern Hospital, Gotenburg; Aronson S, Halmstad Hospital, Halmstad; Jensen D, Helsingborg Hospital, Helsingborg; Winiarski J, Huddinge Hospital, Huddinge; Berglund K, Hudiksvall Hospital, Hudiksvall; Jonsson N-O, Jönköping Hospital, Jönköping; Cervin T, Kalmar Hospital, Kalmar; Malmport S, Karlskrona Hospital, Karlskrona; Berg A, Central Hospital, Karlstad; Nilsson H, Kristianstad Hospital, Kristianstad; Ludvigsson J, Linköping Hospital, Linköping; Wiebe T, University Hospital, Lund; Ljung R, Malmö Hospital, Malmö; Tessin I, Mölndal Hospital, Mölndal; Ljungren CG, Norrköping Hospital, Norrköping; Dahlwitz A, Nyköping Hospital, Nyköping; Christensen HO, Skellefteå Hospital, Skellefteå; Wettrell G, Kärnsjukhuset, Skövde; Berglund M, Sollefteå Hospital, Sollefteå; Appelby G, Sundsvall Hospital, Sundsvall; Eriksson M, Uddevalla Hospital, Uddevalla; Erik Forestier, University Hospital, Umeå; Kreuger A, University Hospital Uppsala; Michanek K, Visby Hospital, Visby; Samuelsson G, Trollhättan Hospital, Trollhättan; Eriksson B, Västervik Hospital, Västervik; Berg T, Västerås Hospital, Västerås; Hedling L, Växjø Hospital, Växjø; Forsberg T, Ängelholm Hospital, Ängelhjolm; Wranne L, Örebro Medical Center, Örebro; Kriström B, Örnsköldsvik Hospital, Örnsköldsvik; and Gustafsson G, Östersund Hospital, Östersund. [Context Link]

Key Words: Child; Circadian rhythm; Drug monitoring; Erythrocyte chemistry; Food; Leukemia, acute lymphocytic; 6-Mercaptopurine; Methotrexate; Polyglutamic acid; Thioguanine nucleotides

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IMAGE GALLERY

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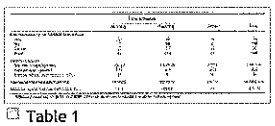

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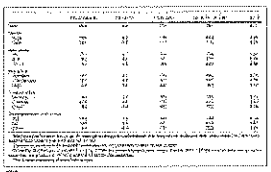

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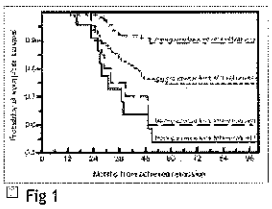

☐ Fig 1

Back to Top