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Benefit of high-dose methylprednisolone in comparison with conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic leukemia for long-term follow-up

S Yetgin[1], MA Tuncer[1], M Çetin[1], F Gümrük[1], I Yenicesu [1], B Tunç[1], AF Öner[1], H Toksoy[1], A Koç,[1], D Aslan[1], E Özyürek[1], L Olcay[1], L Atahan[2], E Tunçbilek[2] and A Gürgey[1]

[1]*Department of Pediatric Hematology, Hacettepe University, Ihsan Dogramaci Children's Hospital, Ankara, Turkey;* [2]*Department of Radiation Oncology, Hacettepe University, Ankara, Turkey; and* [3]*Department of Genetics, Hacettepe University, Ihsan Dogramaci Children's Hospital, Ankara, Turkey*

Eight-year event-free survival (EFS) was evaluated in 205 patients with acute lymphoblastic leukemia (ALL), to consider the efficacy of high-dose methylprednisolone (HDMP) given during remission induction chemotherapy between 1 and 29 days. The St Jude Total XI Study protocol was used after some minor modifications in this trial. Patients were randomized into two groups. Group A (n = 108) received conventional dose (60 mg/m²/day orally) prednisolone and group B (n = 97) received HDMP (Prednol-L, 900–600 mg/m² orally) during remission induction chemotherapy. Complete remission was obtained in 95% of the 205 patients who were followed-up for 11 years; median follow-up was 72 months (range 60–129) and 8-year EFS rate was 60% overall (53% in group A, 66% in group B). The EFS rate of group B was significantly higher than of group A (P = 0.05). The 8-year EFS rate of groups A and B in the high-risk groups was 39% *vs* 63% (P = 0.002). When we compared 8-year EFS rate in groups A and B in the high-risk subgroup for both ages together ⩽2 or ⩾10 years, it was 44% *vs* 74%, respectively. Among patients in the high-risk subgroup with a WBC count ⩾50 × 10⁹/l, the 8-year EFS was 38% in group A *vs* 58% in group B. During the 11-year follow-up period, a total of 64 relapses occurred in 205 patients. In group A relapses were higher (39%) than in group B (23%) (P = 0.05). These results suggest that HDMP during remission-induction chemotherapy improves the EFS rate significantly for high-risk patients in terms of the chances of cure.
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Introduction

With the current therapeutic regimens, more than 70% of childhood acute lymphoblastic leukemia (ALL) patients are cured.[1] Recent ALL studies are mostly focused on determining relapse risk factor in regard to treatment protocols. Most treatment failures in childhood ALL seem to result from inadequate initial reduction of the leukemic clone and the acquisition of drug resistance by residual leukemia. In the categorization of risks in childhood ALL, clinical factors (white blood cell (WBC), age, gender and speed of early response to therapy) are combined with identification of cytogenetic and molecular genetic abnormalities and, most recently, with the monitoring of minimal residual disease by molecular methods.[2–7] The aim of such strategies is to identify patients at high risk for treatment failure, who may benefit from more intensive treatment and those in whom treatment may, perhaps, be safely reduced to avoid possible long-term morbidity.

Correspondence: S Yetgin, Hacettepe University, Department of Pediatric Hematology, Ihsan Dogramaci Children's Hospital, 06100, Ankara, Turkey; Fax: +90 312 324 1681
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The profound inhibitory effect of glucocorticoids on cells of lymphoid origin and their high efficacy in killing or inhibiting the growth of malignant lymphocytes have been known for decades. Glucocorticoids mediate their direct effect on a cell through a highly specific cytoplasmic receptor.[8] By interaction of the glucocorticoid–receptor complex with the genome, the initiation of transcription of the glucocorticoid responsive gene is modulated, thereby inducing a specific cellular response.[9,10] The magnitude of this response is determined in part by the level of circulating hormones and in part by the level of functional receptor proteins.[11,12]

Although there are limited reports, successful results with high-dose corticosteroid or methylprednisolone (HDMP) have been obtained in different hematological diseases and different types of leukemia with different stages.[13–19] In this study, our intention was the treatment of ALL with St Jude Total Therapy Study XI protocol (Total XI Study),[20] subjected to minor modifications in which use of HDMP was compared to conventional-dose prednisolone, during the remission induction therapy period in two randomized and stratified patient groups. We have previously reported that the 3-year event-free survival (EFS)[21] was significantly higher in the HDMP-treated group in the same group of patients. In the present report, we assessed the rate of cure chance of ALL patients with these therapeutic approaches.

Patients and methods

From March 1991 to March 1997, 265 consecutive children younger than 18 years of age were newly diagnosed with ALL in our clinic. Fifty-five patients were excluded from randomization for various reasons (refusal of therapy n = 8, request for therapy in the hospitals of their home town n = 47). Five patients were not tolerant for HDMP within 1–2 days. The remaining patients were randomized according to odd and even file numbers into two groups to be given conventional dose (60 mg/m²/day orally group A) and HDMP (Prednol-L 900–600 mg/m²/day orally group B), respectively (Table 1). Those patients who were available for follow-up were enrolled in the Total XI Study protocol, after parental consent was obtained. The diagnosis was based on morphologic and cytochemical evaluation of bone marrow (BM) smear as well as immunophenotyping by flow cytometer (FACScan; Becton Dickinson, San Jose, CA, USA) with a panel of monoclonal antibodies. Cases were classified as B cell precursor, T cell, common, null cell and mixed type as previously described.[21] All phenotypes, with the exception of B phenotype and L3, were included in the study. BM samples were processed using the method of Spurbeck *et al*[22] and classified on the basis of numerical and structural abnormality according to the international system for human cytogenetic nomenclature.[23]

Table 1 Early treatment

Drug	*Dose (route)*	*Given on days*
Prednisolone (group A)	60 mg/m^2 (p.o.)	1–29
Methylprednisolone (group b)	900 mg/m^2 (p.o.)	1–7
	600 mg/m^2 (p.o.)	8–15, 17, 19, 21, 23,25, 27,29
Vincristine	1.5 mg/m^2 (i.v.)	1, 8, 15, 22
Daunorubicin	30 mg/m^2 (i.v.)	2, 8, (15)[a]
L-asparaginase	200 U/kg (i.v, i.m.)	3, 4, 6, 8, 10, 12, (15, 17, 19)[a]
Cytosine arabinoside	300 mg/m^2 (i.v.)	22, 25, 29
Cyclophosphamide	300 mg/m^2 (i.v.)	36,43
Etoposide	3–6 mg/kg (i.v.)	36, 43
Methotrexate (i.t.)	12[b], 10[c], 8[d] mg	2, 22, 43
Prednisone (i.t.)	24[b], 20[c], 16[d] mg	2, 22, 43
Cytosine arabinoside(i.t.)	36[b], 30[c], 24[d] mg	2, 22, 43
High-dose methotrexate[e]	50 mg/kg (i.v.)	50, 57

p.o., orally; i.v., intravenous; i.m., intramuscular, i.t., intrathecal.
[a]The doses in parentheses are given if bone marrow is not in remission on day 15.
[b]Given if the patient is >3 years old.
[c]Given if the patient is 1–3 years old.
[d]Given if the patient is <1 years old.
[e]Followed by leucoverin rescue, as with Total Study XI.

All patients were classified to low or high risk of relapse groups based on the criteria of the Total XI study. An initial WBC count $\geqslant 100 \times 10^9$/l or two or more unfavorable prognostic features (specific translocation in leukemic cells, WBC count $\geqslant 25 \times 10^9$/l, age $\leqslant$2 years or $\geqslant$10 years, initial central nervous system (CNS) leukemia, CALLA(–) T or B immunophenotype, extramedullary leukemia, hypodyploid chromosome and lack of BM remission (>5% blasts, M2) on day 15 of induction chemotherapy) were accepted as predictive factors for a high risk. The total XI Study protocol[20] was adapted with minor modifications. HDMP was administered to group B during remission induction (900 mg/m^2/day orally was administered on days 1–7 and 600 mg/m^2/day was given on days 8–15, 17, 19, 21, 23, 25, 27 and 29) (Table 1). The protocols are similar except with respect to these protocol features: two rather than three doses of epipodophyllotoxin (etoposide) during the induction treatment. Etoposide was not given simultaneously with Ara-C, and etoposide with cyclophosphamide was given later, at days 36 and 43 because of the high risk of infection in our country. Etoposide and intrathecal prednisolone were used in place of teniposide and the intrathecal form of hydrocortisone used in the Total XI Study regimen, respectively, because the latter two were not available. If marrow aspirates collected on day 15 of induction therapy contained leukemic blasts, additional doses of drugs, as documented in Table 1, were given, as in the Total XI Study. Patients who did not attain complete remission after induction/consolidation with methotrexate were taken out of the study. Since DNA index could not be studied and cytogenetic studies could only be done in 30% of our patients, the maintenance therapy was the same in the low- and high-risk groups as the treatment in group 2 of the St Jude Study XI.[20] Briefly, it consisted of four pairs of drugs rotated weekly over 120 weeks as follows: (1) intravenous etoposide 300 mg/m^2 + cyclophosphamide 300 mg/m^2 once a week; (2) oral mercaptopurine 75 mg/m^2/day for 7 days + intramuscular methotrexate 40 mg/m^2 once a week; (3) intravenous etoposide 300 mg/m^2 + cytarabine 300 mg/m^2 once a week; (4) oral prednisolone 60 mg/m^2/day for 7 days + intravenous vincristine 1.5 mg/m^2 once a week. Cranial irradiation (1800 cGy) and five intrathecal injections were added for high-risk patients as soon as possible after consolidation therapy. This approach was adapted after reviewing the results of the Total XI Study protocol regarding cranial radiotherapy at 1 year of maintenance therapy for patients >2 years of age. Cranial irradiation (2400 cGy) was given to patients with CNS leukemia. Reasons for exclusion from the study were failure to attain complete remission or BM relapses. Those with extramedullary relapses remained in the study, however, with repeated reinduction therapy as in the Total XI Study. These patients were considered to be treatment failures for analysis of event-free survival (EFS). All details of risk criteria, complete remission, CNS leukemia at diagnosis and therapy protocol have been given in our previously published report on 3-year EFS in a section of this same group of patients.[21]

Statistics

Event-free survival was estimated by Kaplan–Meier analysis of data updated to March 2002. Differences in survival rates were assessed by the log-rank test. EFS was calculated from the first day of treatment to the time of analysis or to the first event (early death, resistance, relapse, death during complete remission or secondary malignancy). Differences in the distribution of variables among patient subsets were analyzed using the chi-square test for categorized variables. Multivariate analysis with the Cox proportional-hazards model was used to independently determine significant prognostic factors. The differences between the steroid-induced side-effects in the two groups were assessed by likelihood ratio test.

Results

The presenting clinical and laboratory characteristics of the 205 patients are shown in Table 2. The median age was 5.5 years (range 11 months–16 years) and the median WBC count was 11 (range 1–850) $\times 10^9$/l. One hundred and ninety-four patients of the 205 (95%) entered complete remission. One hundred and twenty-six (64%) of the 198 patients (seven early deaths were excluded) achieved M1 marrow (<5% blasts) on day 15 of induction therapy. The median follow-up time was 72 (range 60–129) months.

Group A (n = 108; median age 5, range 11 months–16 years) received conventional-dose prednisolone and group B (n = 97; median age 6, range 15 months–15 years) was given HDMP. The median WBC count for group A was 13 (range 1–750) $\times 10^9$/l and for group B 10.2 (range 1–850) $\times 10^9$/l. There was no significant difference between groups A and B in terms of remission rate, age, sex, WBC count, immunophenotype, FAB classification or in the percentage of patients who achieved BM remission by day 15. In group A, the number of patients in the 0–2 year age group was higher but not statistically significant. In comparison of groups A and B the number of high-risk patients was significantly greater in group B than A (P = 0.01) (Table 2).

The 8-year EFS rates (s.e.) of all 205 patients (groups A and B), group A alone and group B alone were 60 (5)%, 53 (5)% and 66 (5)%, respectively (P = 0.05 between groups A and B) (Table 3) (Figure 1a). In high-risk patients, it was 39% for group A and 63% for group B which was a significant difference (P = 0.002) (Figure 1b), but there was no difference

Table 2 Clinical and laboratory characteristics of patients (n = 205)

	Total		Group A		Group B	
	n	%	*n*	%	*n*	%
Risk[a]						
Lower	66	32	42	39	24	25[a]
Higher	139	68	66	61	73	75
Age, years						
⩽2	23	11	15	14	8	8
>2 <10	136	66	66	61	70	72
⩾10	46	23	27	25	19	20
Sex						
Male	119	58	58	54	61	63
Female	86	42	50	46	36	37
Leukocyte count (× 10^9/l)						
0–24	138	67	66	61	72	74
25–49	20	10	13	12	7	7
50–99	24	12	14	13	10	10
>100	23	11	15	14	8	9
Day 15 bone marrow						
<5% blasts	126	64	67	66	59	64
⩾5% blasts	56	28	31	30	25	26
Unknown	16	8	6	6	10	11
Immunophenotype						
CALLA-positive B	65	32	35	33	30	31
CALLA-negative B	17	8	7	6	10	11
CALLA-positive T	9	4	8	7	1	1
CALLA-negative T	26	13	18	17	8	8
CALLA-positive	24	12	9	8	15	15
Null	31	15	12	11	19	20
Mixed lineage leukemia	15	7	6	6	9	9
Unknown	18	9	13	12	5	5
FAB classification						
L1	106	52	59	55	47	48
L2	99	48	49	45	50	52
CNS leukemia at diagnosis	3	1.4	1	1	2	2
Mediastinal infiltration at diagnosis	17	8	10	9	7	7
CNS + mediastinal infiltration at diagnosis	1	0.5	1	1	—	—
Bone involvement	37	18	18	17	19	20

[a]Number of high-risk patients was significantly higher than those at lower risk in group B.

between groups A and B for the low-risk patients (P = 0.8). EFS for patients with age-related risk (age ⩽2 or ⩾10 years) was 44% in group A (n = 42) and 74% in group B (n = 28) (P = 0.05). Among patients in the other high-risk subgroup with a WBC count ⩾50 × 10^9/l, the 8-year EFS was 38% in group A (n = 29) *vs* 58% in group B (n = 20) (P = 0.07). When we compare high-risk patients on the basis of T and B immunophenotypes, EFS were 19% and 43% in group A, 60% and 77% in group B, respectively. EFS was significantly higher for T and B immunophenotypes in group B when compared to group A (P = 0.07, P = 0.04, respectively). When the EFS rate regarding M1/M2 status of remission was considered the 8-year EFS rate was 61% in group A *vs* 78% in group B for M1 (P = 0.05) and 28% in group A *vs* 58% in group B for M2 (P = 0.04). Although there was a statistically significant difference between M1/M2 EFS status in group A (P = 0.04), it was comparably similar in group B (Table 3). There was also no difference in EFS rate between the two groups with regard to other parameters such as sex or FAB classification of ALL. In the multivariate analysis in high-risk groups, HDMP is an independent effective factor on EFS and significantly associated with better prognosis (P = 0.05).

Relapse rate (Table 4) was higher in group A (n = 42/108) with 39% than in group B (n = 22/97) with 23% (P = 0.05). A total of 64 relapses occurred over the 11-year follow-up interval (March 1991–March 2002) in 205 patients: 48, 15 and one in the BM, CNS and testes, respectively. There was a significant difference between the groups with regard to BM relapses; CNS relapses were equal. Thirty-nine (61%) of 64 relapses were seen during treatment at a median time of 12 (range 5–28) months. Relapses occurring during treatment and after cessation of treatment were 25 and 17 patients in group A and 14 and 8 in group B, respectively. After cessation of therapy, 13 (20%) patients relapsed during the first 12 months and 12 (19%) patients between 14 and 63 months. CNS relapses (eight in group A and seven in group B) occurring during treatment and after cessation of treatment were five and three for group A and five and two for group B, respectively. In 13 patients, CNS relapses occurred before cranial radiotherapy, which had been postponed for 1 year because of the patients' ages (⩽2) and for technical reasons, ie low capacity of the radiotherapy department.

The median duration of the induction period in group A was 66 (range 44–98) days *vs* 75 (range 44–120) in group B. The number of infectious episodes per patient was 0.81 and 0.84 in group A and B, respectively. Side-effects of corticosteroid treatment are shown in Table 5. There was no significant difference between the two groups. Five patients showed signs of distolerance to HDMP within 1–2 days and were therefore excluded from this study. Comparison of bone mineral density between the two groups revealed no significant difference (P = 0.6). Analyses were performed by using the the dexa method in 29 patients of group A and 26 patients of group B. (This study will be reported soon.) Secondary acute myeloblastic leukemia (AML) occurred in one patient in group A and in two patients in group B. In these three patients, all known to have high-risk criteria and B immunophenotype, secondary AML was diagnosed at 27, 41 and 41 months, respectively.

Chromosomal studies could be performed in 67 out of 205 patients. Abnormal chromosomal findings were documented in 13 patients as follows: five hypodiploid (four patients in group B), four hypodiploid + tetraploid (all in group B), one tetraploid, two Philadelphia chromosome-positive (Ph+) and one t(8;21) (all in group A).

Discussion

The prominent result of this study was the improved efficacy of HDMP applied during remission induction chemotherapy (days 1–29) on EFS and on relapse rate of ALL patients. In the HDMP group, the 8-year EFS rate was 66% in 97 *vs* 53% in 108 patients who received conventional-dose steroid (P = 0.05). Although a significantly greater number of high-risk patients were included in the HDMP group, the EFS rate was significantly higher in this group (P = 0.002). The EFS rate was not only in total significantly higher in the HDMP-treated group than in patients treated with conventional-dose prednisolone, but also in high-risk and high-risk subgroup patients.

Table 3 Eight-year event-free survival in patient groups

	Group A		Group B		P value	Total (A + B)	
	EFS (s.e.) %	n	EFS (s.e.) %	n		EFS (s.e.)%	n
Total	53 (5)	108	66 (5)	97	0.05	60 (5)	205
High risk	39 (7)[1]	66	63 (6)[3]	74	0.002		
Low risk	71 (7)[2]	42	74 (9)[4]	23	0.8		
Age ⩽2 years ⩾10 years	44 (8)	42	74 (9)	28	0.05		
WBC (50×10^9/l	38 (9)	29	58 (11)	20	0.07		
High risk with T cell	19 (10)	16	60 (15)	10	0.07		
High risk with B cell	43 (13)	14	77 (9)	22	0.04		
Remission on day 15 (M1)	61 (6)[5]	67	78 (5)[7]	59	0.05		
Non remission on day 15 (M2)	28 (9)[6]	31	58 (12)[8]	25	0.04		

P values in comparison of the following parameters: 1–2 = 0.03; 3–4 = 0.6; 5–6 = 0.04; 7–8 = 0.4.

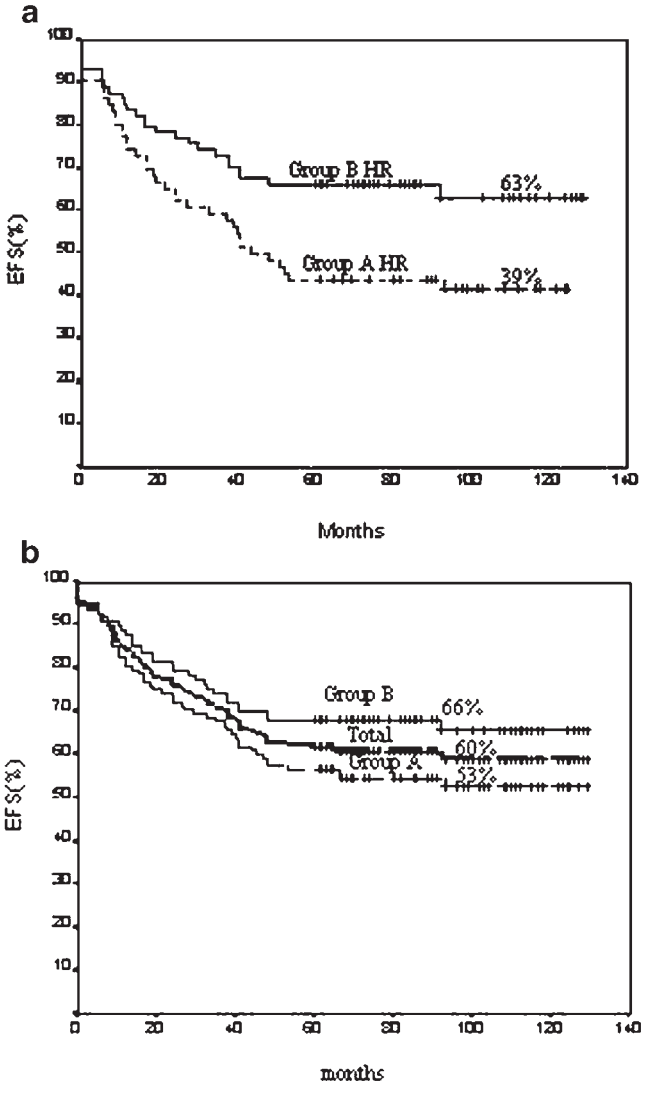

Figure 1 (a) Eight-year event-free survival (EFS) rate in group A and group B patients and in the total group. (b) Eight-year event-free survival (EFS) rate of high-risk patients in group A and group B.

There was also a clear difference in the subgroup of patients with WBC ⩾50×10^9/l between groups A and B ($P = 0.07$) (Table 3). The comparable EFS rates of low-risk patients in both groups showed the importance of the effects of HDMP especially on high-risk patients. These data prompted us to consider the EFS rate in low- and high-risk patients in groups A and B separately in more detail. As a result the EFS rate in each group with respect to (1) low- and high-risk and (2) day 15 remission (M1) and non-remission (M2) were compared. Although significant differences were found in group A, similar levels were found in group B for each parameter. After analysis of the EFS rate for different immunophenotype groups, EFS was found to be significantly higher in group B for high-risk T and B phenotypes. All these results pointed to the fact that the HDMP efficacy tended to be greater in patients with high-risk criteria.

Relapses were also reduced by HDMP therapy during the 11-year follow-up of 205 patients (Table 4). However, there was no change observed in the CNS relapse rate, possibly due to the limited number of patients in our study.

Positive results with HDMP therapy alone have been found by Ryalls *et al*[15] in patients with ALL relapsing in the BM, the CNS or testes. Results of the ALL-BFM 86 protocol, in which therapy for all patients started with a 7-day monotherapy with prednisone and intrathecal methotrexate dose on day 1, showed that the number of blasts per microliter in peripheral blood on day 8 was inversely correlated with the cumulative prednisone dose.[24] A recent study (planned at the same time with our study), has shown that although a dose–response relationship between the use of prednisolone (2 mg/kg/day) dexamethasone (6, 18 and 150 mg/m^2/day) and BM and PB blast reduction was significant, the effect of dose on EFS rate was not found to be significant.[25] Retrospectively, we assessed the effect of HDMP and conventional–dose prednisolone during the first week of the induction period on the blast cell reduction rate in groups A and B. The effect of HDMP on blast reduction rate and EFS was significantly higher in group B (HDMP group) ($P = 0.03$ and $P = 0.05$, respectively). (This study will be reported.)

In our clinic, acceleration of leukocyte recovery in ALL children after administration of short-course HDMP has been shown.[16] CD34 antigen expressing cells have clearly been increased in acute leukemia patients treated with HDMP.[17,26] However, experience with high-dose steroid administration in leukemic patients is limited and the few studies performed were non-randomized and used historical retrospective controls.[14–19] They did not compare conventional-dose steroid

Table 4 Sites of treatment failure in 205 randomized patients

	Total			*Group A*		*Group B*	
	n	*High R*	*Low R*	*High R*	*Low R*	*High R*	*Low R*
No. of total relapses	64	50	14	32	10	18	4
No. of BM relapses	48	38	10	26	7	12	3
No. of CNS relapses	15	10	5	5	3	6	1
No.of testes relapse	1	1	—	1	—	—	—
No. of death in remission[a]	5	5	—	2	—	3	—
No. of secondary AML	3	3	—	1	—	2	—

The comparison of group A with group B: in total relapse $P = 0.05$; BM relapse $P = 0.05$.
[a]Encephalopathy in two cases, meningococcemia in one case, cardiomyopathy in one case, pulmonary hemorrage in one case.

Table 5 Side-effects of steroids in patients

Side-effects	*Group A (n = 108)*		*Group B (n = 97)*		*Total n*
	n	*%*	*n*	*%*	
Hyperglycemia	6	43	8	57	14
GI bleeding	1	20	4	80	5
Hypertension	2	14	12	86	14
Cushingoid appearance	5	38	8	62	13
Bradicardi, arrhythmia	4	44	5	56	9
Myalgia	3	37	5	63	8
Abdominal pain	3	33	6	67	9
Behavioral disturbance	0	0	3	100	3
Liver enlargement	1	8	11	92	12

treatment with an intensive chemotherapeutic regimen and results were not obtained for a longer period of time.

Previous studies have shown that the effect of steroid on leukemic cell death is related to glucocorticoid receptor (GR) occupation,[25,27] the presence of non-functional receptor protein,[11,12] and lineage-specific differences in GR levels.[28] Low level of GRs in ALL tended to correlate with high risk.[29] In contrast a small number of patients with a high level of GR showed no response to therapy.[9,29] Thus other factors may also contribute to or modify the response to steroids, such as repression/or activation of transcription factors and interaction through other transductin pathways.[30,31] The effect of different factors on individual clones of leukemic cells may predict the resistance or sensitivity of those cells. In our results, the benefits from HDMP suggest that the megadose of glucocorticoids may be effective on the non-functional receptors or GR modifying factors.

This prospective and randomized study strongly suggests that HDMP has a higher efficacy in the long run, ie a greater cure rate than conventional-dose prednisolone administration used in induction therapy of ALL patients. The HDMP in induction therapy induces a prolonged remission duration and the EFS rate is quite comparable with the Total XI Study EFS rate. An overall 60% 8-year EFS rate was obtained with the Total XI Study protocol *vs* rates of 11%[32] and 43%[19] for 3- and 5-year EFS obtained in our previous conventional ALL therapy trial. However, there is still some discrepancy between the cure rate obtained in the present study (53%) and the St Jude Total XI study group (69.3%),[33] although the same regimens and conventional-dose steroids were used. It should be kept in mind that most of the patients in our group were from poor socio-economic levels. There were often infections in these patients which led to delays in chemotherapy resulting in prolonged duration of the induction period and of the period between courses of therapy, in addition to immune suppression effect of infections.[32,34,35]

The CNS relapse rate (7.3% of 205 patients) was similar to the Total XI Study result (5.9%) and patients were equally distributed within groups (eight and seven, respectively). Four patients were ⩽2 years, which, in the case of MLL gene abnormality, could be the most important risk factor for CNS relapse. Cranial irradiation postponed for 1 year was also a factor known to result in a higher CNS relapse rate. This result highlights, however, that HDMP did not affect CNS relapse. It is important to report that testes relapse was seen in one patient at 6 months follow-up after completed maintenance treatment, a result of intensive chemotherapy of the Total XI Study protocol which has also been seen in previous experiences.

Secondary AML rate was not higher than in the Total XI Study.

Side-effects of HDMP as presented in Results, are generally tolerable and could be corrected by standard therapeutic approaches. Complications of HDMP did not result in any deaths, but five patients who could not tolerate steroids were excluded from the study. Another side-effect was hyperglycemia in which L-asparaginase may have been an inducing factor.[36] At the conclusion of a long follow-up period there was no difference between groups treated with HDMP or conventional-dose corticosteroids with regard to glucocorticoid side-effects such as bone mineral density.

In conclusion, as a first randomized and prospective study assessing chances of cure, we suggest here that HDMP therapy during remission induction increases cure rate and decreases relapse rate. The most important point is that the effect of HDMP was clearly observed not only in high-risk patients but also in patients having any high-risk criteria and it seems to be effective on the rapid reduction of blast cells. Consequently, a megadose of glucocorticoid is needed in high-risk patients to affect blast death.

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References

1 Pui CH, Evans WE. Acute lymphoblastic leukemia. *N Engl J Med* 1998; **339**: 605–615.
2 Pui CH. Childhood leukemias. *N Engl J Med* 1995; **332**: 1618–1630.
3 Pui CH. Recent advances in the biology and treatment of childhood acute lymphoblastic leukemia. *Curr Opin Hematol* 1998; **5**: 292–301.
4 Gaynon PS, Desai AA, Bostrom BC, Hutchinson RJ, Lange BJ, Nachman JB, Reaman GH, Sather HN, Steinherz PG, Trigg ME, Tubergen DG, Uckun FM. Early response to therapy and outcome in childhood acute lymphoblastic leukemia: a review. *Cancer* 1997 **80**: 1717–1726.
5 Pui CH, Crist WM, Look AT. Biology and clinical significance of cytogenetic abnormalities in childhood acute lymphoblastic leukemia. *Blood* 1990; **76**: 1449–1463.
6 Manera R, Ramirez I, Mullins J, Pinkel D. Pilot studies of species-specific chemotherapy of childhood acute lymphoblastic leukemia using genotype and immunophenotype. *Leukemia* 2000; **14**: 1354–1361.
7 Panzer-Grumayer ER, Schneider M, Panzer S, Fasching K, Gadner H. Rapid molecular response during early induction chemotherapy predicts a good outcome in childhood acute lymphoblastic leukemia. *Blood* 2000; **95**: 790–794.
8 Thompson EB. Apoptosis and steroid hormones. *Mol Endocrinol* 1994; **8**: 665–673.
9 Moalli PA, Rosen ST. Glucocorticoid receptors and resistance to glucocorticoids in hematologic malignancies. *Leuk Lymphoma* 1994; **15**: 363–374.
10 Beato M. Gene regulation by steroid hormones. *Cell* 1989; **56**: 335–344.
11 Gustafsson JA, Carlstedt-Duke J, Poellinger L, Okret S, Wikstrom AC, Bronnegard M, Gillner M, Dong Y, Fuxe K, Cintra A. Biochemistry, molecular biology, and physiology of the glucocorticoid receptor. *Endocr Rev* 1987; **8**: 185–234.
12 Gehring U. Genetics of glucocorticoid receptors (review). *Mol Cell Endocrinol* 1986; **48**: 89–96.
13 Özsoylu S. High dose intravenous methylprednisolone in hematologic disorders. *Hematol Rev* 1990; **4**: 197–207.
14 Shamson E, Miller S. Critical evaluation of massive steroid therapy of acute leukemia. *N Engl J Med* 1962; **266**: 1354–1358.
15 Ryalls MR, Pinkerton CR, Meller ST, Talbot D, McElwain TJ. High-dose methylprednisolone sodium succinate as a single agent in relapsed childhood acute lymphoblastic leukemia. *Med Pediatr Oncol* 1992; **20**: 119–123.
16 Hiçsönmez G, Onat N, Albayrak D, Yetgin S, Özsoylu S. Acceleration of leukocyte recovery by administration of short-course high-dose methylprednisolone in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 1991; **8**: 193–197.
17 Özbek N, Yetgin S, Tuncer M. Effects of G-CSF and high-dose methylprednisolone on peripheral stem cells, serum IL-3 levels and hematological parameters in acute lymphoblastic leukemia patients with neutropenia: a pilot study. *Leuk Res* 2000; **24**: 55–58.
18 Hiçsönmez G, Özsoylu S, Onat N, Zamani VP, Gümrük F, Tuncer M. High dose methylprednisolone in resistant and relapsed children with acute lymphoblastic leukemia. *Med Pediatr Oncol* 1994; **22**: 68–69.
19 Hiçsönmez G, Gümrük F, Zamani PV, Tuncer MA, Yetgin S, Gürgey A, Atahan L, Özsoylu S. High-dose methylprednisolone for children with acute lymphoblastic leukemia and unfavorable presenting features. *Eur J Haematol* 1997; **58**: 26–31.
20 Rivera GK, Raimondi SC, Hancock ML, Behm FG, Pui CH, Abromowitch M, Mirro J Jr, Ochs JS, Look AT, Williams DL, Murphy SB, Dahl GV, Kalwinsky DK, Evans WE, Kun LE, Simone JV, Crist WM. Improved outcome in childhood acute lymphoblastic leukemia with reinforced early treatment and rotational combination chemotherapy. *Lancet* 1991; **337**: 61–66.
21 Yetgin S, Gürgey A, Tuncer AM, Çetin M, Özbek N, Sayli T, Güler E, Kara A, Olcay L, Duru F, Gümrük F, Atahan L, Tunçbilek E. A comparison of the effect of high-dose methylprednisolone with conventional-dose prednisolone in acute lymphoblastic leukemia patients with randomization. *Leuk Res* 1998; **22**: 485–493.
22 Spurbeck JL, Carlson RO, Allen JE, Dewald GW. Culturing and robotic harvesting of bone marrow, lymph nodes, peripheral blood, fibroblasts, and solid tumors with *in situ* techniques. *Cancer Genet Cytogenet* 1988; **32**: 59–66.
23 Mitelman F (ed.). *An International System for Human Genetic Nomenclature*. Karger: Basel, 1995.
24 Reiter A, Schrappe M, Ludwig WD, Hiddemann W, Sauter S, Henze G, Zimmermann M, Lampert F, Havers W, Niethammer D. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. *Blood* 1994; **84**: 3122–3133.
25 Schwartz CL, Thompson EB, Gelber RD, Young ML, Chilton D, Cohen HJ, and Sallan SE. Improved response with higher corticosteroid dose in children with acute lymphoblastic leukemia. *J Clin Oncol* 2001; **19**: 1040–1046.
26 Çetin M, Hiçsönmez G, Tuncer AM, Kansu E, Canpinar H. The effect of short-course high-dose corticosteroid therapy on peripheral blood CD34+ progenitor cells in children with acute leukemia. *Exp Hematol* 1996; **24**: 1191–1194.
27 Thomson EB, Harmon JB, Zawydiwski R. Corticosteroid effects on an ALL cell live: a model for understanding steroid therapy. In: Murphy SB, Gilbert JR (eds). *Leukemia Research. Advances in Cell Biology and Treatment*. Elseiver Science: New York, NY, 1983, pp 157–169.
28 Quddus FF, Leventhal BG, Boyett JM, Pullen DJ, Crist WM, Borowitz MJ. Glucocorticoid receptors in immunological subtypes of childhood acute lymphocytic leukemia cells: Pediatric Oncology Group Study. *Cancer Res* 1985; **45**: 6482–6486.
29 Estlin EJ, Ronghe M, Burke GA, Yule SM. The clinical and cellular pharmacology of vincristine, corticosteroids, L-asparaginase, anthracyclines and cyclophosphamide in relation to childhood acute lymphoblastic leukaemia. *Br J Haematol* 2000; **110**: 780–790.
30 Jonat C, Rahmsdorf HJ, Park KK, Cato AC, Gebel S, Ponta H, Herrlich P. Antitumor promotion and antiinflammation: down-modulation of AP-1 (Fos/Jun) activity by glucocorticoid hormone. *Cell* 1990; **62**: 1189–1204.
31 Stocklin E, Wissler M, Gouilleux F, Groner B. Functional interactions between Stat5 and the glucocorticoid receptor. *Nature* 1996; **383**: 726–728.
32 Hiçsönmez G, Özsoylu S, Yetgin S, Zamani V, Gürgey A, Atahan I. Prognosis in 262 Turkish children with acute lymphocytic leukemia. *Turk J Pediatr* 1982; **24**: 159–167.
33 Pui C-H, Boyett JM, Rivera GK, Hancock ML,Sandlund JT, Riberio RC, Rubnitz JE, Behm FG, Raimondi SC, Gajjar A, Razzouk B, Campana D, Kun LE, Relling Mvand Evans WE. Long-term results of total therapy studies 11,12 and 13A for children with acute lymphoblastic leukemia at St Jude Children's Research Hospital. *Leukemia* 2000; **14**: 2286–2294.
34 Walters TR, Bushore M, Simone J. Poor prognosis in Negro children with acute lymphocytic leukemia. *Cancer* 1972; **29**: 210–214.
35 Hiçsönmez G, Özsoylu S, Yetgin S, Zamani V, Gürgey A. Poor prognosis of childhood acute lymphoblastic leukaemia. *Br Med J* 1983; **286**: 1437.
36 Çetin M, Yetgin S, Kara A, Tuncer AM, Günay M, Gümrük F, Gürgey A. Hyperglycemia, ketoacidosis and other complications of L-asparaginase in children with acute lymphoblastic leukemia. *J Med* 1994; **25**: 219–229.