Substituting Dexamethasone for Prednisone Complicates Remission Induction in Children with Acute Lymphoblastic Leukemia

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Supported in part by Grant CA68484 from the National Cancer Institute.

The authors thank the patients, families, nurses, physicians, study coordinators, and data managers who participate in the DFCI ALL Consortium studies. We also thank Mia Donnelly and Gaylord Garraway for central data management activities.

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Received September 7, 1999; revision received December 6, 1999; accepted December 6, 1999.

BACKGROUND. The authors report the occurrence of fatal or near-fatal sepsis in 16 of 38 children with newly diagnosed acute lymphoblastic leukemia (ALL) treated with a new induction regimen that differed from its predecessor by the substitution of dexamethasone for prednisone.

METHODS. The frequency of septic deaths among 38 children who received multiagent remission induction therapy, including dexamethasone (6 mg/m^2) daily for 28 days (pilot protocol 91-01P), was compared with the frequency of septic deaths among children previously treated (protocol 87-01) and subsequently treated (protocol 91-01) in consecutive Dana-Farber Cancer Institute (DFCI) ALL trials with induction therapy that included 21 and 28 days of prednisone (40 mg/m^2), respectively. Except for dexamethasone in protocol 91-01P, the remission induction agents used were identical in substance to those used in protocol 87-01. Protocol 91-01, the successor 91-01P, was also similar, with the exception of the deletion of a single dose of L-asparaginase.

RESULTS. Sixteen of the 38 children (42%) treated on the DFCI 91-01P had documented gram positive or gram negative sepsis (17 episodes) during remission induction, including 4 toxic deaths (11%). In contrast, there were 4 induction deaths among 369 children (1%) treated on protocol 87-01 ($P = 0.0035$) and 1 induction death among 377 children (<1%) treated on protocol 91-01 ($P = 0.0003$).

CONCLUSIONS. Substitution of dexamethasone for prednisone or methylprednisolone in an otherwise intensive conventional induction regimen for previously untreated children with ALL resulted in an alarmingly high incidence of septic episodes and toxic deaths. Awareness of this complication, considering that the substitution has no apparent benefit in the efficacy of remission induction, argues against its routine use in intensive induction regimens for children with ALL. ***Cancer*** **2000;88:1964–9.** © *2000 American Cancer Society.*

KEYWORDS: dexamethasone, remission induction, acute lymphoblastic leukemia, pediatrics.

Because of their profound lympholytic properties, glucocorticoids have played a major role in the treatment of children with acute lymphoblastic leukemia (ALL).[1–3] The lytic effect of glucocorticoids appears to be mediated through glucocorticoid receptors.[4,5] Binding of the receptors inhibits lymphokine production,[6,7] changes the expression of various oncogenes,[8] and causes both cell cycle arrest[9] and apoptosis.[10,11]

Traditionally, patients with ALL receive daily prednisone for approximately 1 month as a component of multiagent remission induction therapy. Because conventional central nervous system (CNS) preventative therapy resulted in toxic sequelae,[12–15] investigators have

sought alternative methods for CNS treatment. One such alternative has been the substitution of dexamethasone for daily prednisone in some clinical trials based on its superior cerebrospinal fluid penetration.[16–18]

Between August and December 1991, 38 children with newly diagnosed ALL were treated on the Dana-Farber Cancer Institute (DFCI) pilot protocol 91-01P to determine, among other objectives, the feasibility and toxicity of using dexamethasone instead of prednisone throughout all phases of treatment. We report the frequency of toxic induction deaths observed in these 38 children and compare that experience with the toxic induction deaths encountered among a total of 745 children treated on the protocols immediately prior to and following the pilot protocol. The larger trials used prednisone, not dexamethasone, during remission induction therapy.

PATIENTS AND METHODS

Patients

Between 1987 and 1995, 784 children ages ≤18 years with previously untreated ALL were enrolled and treated on 1 of 3 consecutive ALL protocols (87-01, 91-01P, and 91-01). Children were enrolled from the following consortium institutions: DFCI, Boston, Massachusetts; Mount Sinai Medical Center, New York, New York; Hospital Ste. Justine, Montreal, Quebec, Canada; Ochsner Clinic, New Orleans, Louisiana; University of Rochester Medical Center, Rochester, New York; McMaster University Medical Center, Hamilton, Ontario, Canada; Le Centre Hospitalier de L'Universite Lavalle, Ste.-Foy, Quebec, Canada; San Jorge Children's Hospital, Santurce, Puerto Rico; and Maine Children's Cancer Program, Scarborough, Maine. Each protocol was approved by the local institutional review board, and informed consent was obtained from all patients prior to the initiation of treatment.

Treatment

Details of the remission induction therapy are described in Table 1. All patients, regardless of their risk classification, received the same induction. Briefly, remission induction therapy for the 369 patients treated on protocol 87-01 consisted of an investigational window of a single dose of *E. coli-, Erwinia-,* or PEG-asparaginase on Day 1, followed by daily oral prednisone and weekly vincristine for 3 weeks beginning on Day 5, and 2 daily doses of doxorubicin on Days 5 and 6. Methotrexate (40 mg/m^2 or 4 g/m^2, according to randomization) was administered at least 8 hours after the last dose of doxorubicin.

Remission induction therapy for the 38 patients treated on protocol 91-01P consisted of a 3-day investigational window of intravenous (i.v.) glucocorticoids (dexamethasone 6, 18, or 150 mg/m^2/day, or prednisolone 40 mg/m^2/day, according to randomization), followed by daily oral dexamethasone (6 mg/m^2/day) and weekly vincristine for 4 weeks beginning on Day 4, and 2 daily doses of doxorubicin on Days 4 and 5. A single dose of *E. coli* or PEG-asparaginase (according to randomization) was also administered on Day 4, and high dose methotrexate (4 g/m^2) followed the last dose of doxorubicin by at least 8 hours.

The 377 patients enrolled on protocol 91-01 received induction therapy identical to that of protocol 91-01P except for postwindow use of daily prednisone in place of dexamethasone and elimination of asparaginase on Day 4.[19] The modifications in induction therapy from protocol 91-01P to protocol 91-01 were made in response to the high rate of infectious episodes reported in this article. The dose of steroid was not routinely modified or discontinued for septic patients in any of the 3 DFCI protocols.

TABLE 1
DFCI Induction Remission Therapy for Children with ALL

Clinical Study	Therapy
87-01 (n = 369)	Randomized window therapy Day 1: Asp: E. coli 25,000 IU/m^2, Erwinia 25,000 IU/m^2, or PEG-asparaginase 2500 IU/m^2 Conventional induction Days 5–26: Pred 40 mg/m^2/d p.o. × 21 days Vcr 1.5 mg/m^2/wk × 3 doses Day 5: Dox 30 mg/m^2/dose Day 6: Dox 30 mg/m^2/dose Randomize: MTX 40 mg/m^2 or 4 gm/m^2
91-01 Pilot (n = 38)	Randomized window therapy Days 1–3: Predn 40 mg/m^2/day i.v., or Dex 6, 18, or 150 mg/m^2/day i.v. Conventional induction Days 4–32: Vcr 1.5 mg/m^2 × 4 doses Dex 6 mg/m^2/day p.o. × 28 days Day 4: Dox 30 mg/m^2 Randomize Asp: E. coli 25,000 IU/m^2 or PEG 2500 IU/m^2 Day 5: Dox 30 mg/m^2 MTX 4 gm/m^2
91-01 (n = 377)	Randomized window therapy Days 1–3: Predn 40 mg/m^2/day i.v., or Dex 6, 18, or 150 mg/m^2/day i.v. Conventional induction Days 4–32: Vcr 1.5 mg/m^2 × 4 doses Pred 40 mg/m^2/day p.o. × 28 days Day 4: Dox 30 mg/m^2 Day 5: Dox 30 mg/m^2 MTX 4 gm/m^2

Asp: asparaginase; Pred: prednisone; Vcr: vincristine; Dox: doxorubicin; MTX: methotrexate; Dex: dexamethasone; Predn: prednisolone.

TABLE 2
Characteristics of the 38 Patients Treated on 91-01 P

Characteristics	No. of patients	No. (%) with infectious complications	*P* value
Total patients	38	16 (42%)	0.20
Standard risk (DFCI)	17	5 (29%)	
High risk (DFCI)	21	11 (52%)	
Risk group NCI criteria			
Good risk pre-B cell	24	9 (37.5%)	0.59
Poor risk pre-B cell	8	3 (37.5%)	
T-cell age >1 yr	5	3 (60%)	
Infants (<365 days)	1	1 (100%)	
Induction window			
Prednisolone 40 mg/m^2	9	4 (44%)	0.52
Dexamethasone 6 mg/m^2	13	5 (38%)	
Dexamethasone 18 mg/m^2	8	2 (25%)	
Dexamethasone 150 mg/m^2	8	5 (63%)	
WBC ($\times 10^9$/L)			
≤20,000	19	6 (32%)	0.31
>20,000<100,000	14	8 (57%)	
≥100,000	5	2 (40%)	
Age			
<9 yrs	30	10 (33%)	0.038
≥9 yrs	8	6 (75%)	
Immunophenotype			
B lineage	32	12 (38%)	0.14
T lineage	5	4 (80%)	
Unknown	1	—	

DFCI: Dana-Farber Cancer Institute; WBC: white blood cell count.

TABLE 3
Toxicity and Outcome During Induction of 38 Patients Treated on 91-01P

Patient	Bacterial or fungal pathogen	Complication	Onset	Outcome
1	*S. epidermidis*	Sepsis	Day 17	CR
2	*S. aureus*	Sepsis/Pneumonia	Day 12	Died on Day 16
3	*S. aureus*	Sepsis	Day 16	CR
4	*S. epidermidis*	Sepsis	Day 12	CR
		Pneumonia	Day 29	
5	*E. coli*	Sepsis	Day 5	Died on Day 13
6	*Klebsiella*	Sepsis	Day 24	Died on Day 24
7	*S. aureus*	Sepsis	Day 10	CR
8	*S. pneumoniae*	Sepsis	Day 18	CR
9	*S. pneumoniae*	Sepsis	Day 16	CR
	S. epidermidis	Sepsis	Day 26	
10	*S. epidermidis* and *Serratia*	Sepsis	Day 22	CR
11	*Septic shock* (pathogen not identified)	Sepsis	Day 15	Died on Day 15
12	*Enterococcus*	Sepsis	Day 14	CR
13	*Mucor pneumonia*	Pneumonia	Day 12	CR
14	*K. pneumoniae* and *S. aureus*	Sepsis	Day 14	CR
15	*S. aureus*	Sepsis	Day 11	CR
16	*Enterococcus* and *S. aureus*	Sepsis	Day 11	CR

CR: complete response.

Therapy for CNS disease during remission induction was identical in the three studies, and consisted of two doses of intrathecal cytarabine (patients were dosed according to age).

Statistical Analysis

The 784 patients enrolled in the study were considered evaluable for analysis of remission induction until completion of all prescribed induction therapy or death from any cause. Statistical comparisons of the presenting patient features, remission induction rate, and number of deaths encountered in the three studies were analyzed using Fisher exact tests.[20] Event free survival (EFS) and leukemia free survival (LFS) statistics were estimated using the Kaplan–Meier method.[21]

RESULTS

Characteristics of the Patients Treated on 91-01P

The characteristics of the 38 children treated on 91-01P are shown in Table 2. Seventeen children had standard risk features as defined by the DFCI at diagnosis (white blood cell count [WBC] $<20{,}000 \times 10^9$/L, age $\geq$ 2 years $<$ 9 years, the absence of CNS disease, and the absence of a t[9;22][q34;q11] or a T-cell immunophenotype); the remaining 21 patients were designated as high risk.

Remission Induction Toxicity

Bacterial or fungal sepsis or pneumonia was noted during remission induction therapy in 16 of the 38 patients (42%) treated on 91-01P. Four of these patients (11%) died from Gram positive or Gram negative sepsis. Among 5 standard risk children (DFCI criteria) there were 6 episodes of sepsis (including 1 death), and 11 high risk children (DFCI criteria) experienced septic episodes (including 3 toxic deaths) ($P = 0.20$, Table 2). The details of the infectious episodes that occurred on protocol 91-01P are shown in Table 3. The median onset of infectious episodes was 14 days (range, 5–29 days) after therapy was started. No increase in septic deaths were observed according to the treating institution in this multi-institutional study ($P = 0.91$; data not shown).

Differences in the incidence of infectious complications within patient subgroups (including reassignment of patients according to NCI risk criteria) were statistically significant only for age (Table 2; $P = 0.038$), indicating that children ages ≥9 years may be at greater risk of infection. This significant value, how-

TABLE 4
Comparison of Outcome and Toxicity by Protocol

	No. of patients	Toxic induction deaths (%)[a]	Failure from refractory disease[b] (%)	Overall remission induction rate[c]
87-01	369	4 (1.1%)	9 (2.4%)	96.5%
91-01P	38	4 (10.5%)	0 (0%)	89.5%
91-01	377	1 (0.3%)	5 (1.3%)	98.4%

[a] *P* values for toxic induction deaths rates are: $P = 0.0035$ for 91-01P vs. 87-01; $P = 0.0003$ for 91-01P vs. 91-01; $P = 0.21$ for 87-01 vs. 91-01.

[b] *P* values for failure from refractory disease are: $P = 0.41$ for 91-01P vs. 87-01; $P = 0.62$ for 91-01P vs. 91-01; $P = 0.29$ for 87-01 vs. 91-01.

[c] *P* values for remission induction rate are: $P = 0.06$ for 91-01P vs. 87-01; $P = 0.008$ for 91-01P vs. 91-01; $P = 0.11$ for 87-01 vs. 91-01.

ever, may have been due to the small number of patients evaluated. No appreciable influence was detected between the randomized dose of glucocorticoid administered during the investigational window and subsequent infectious complications ($P = 0.52$).

Remission Induction Outcome by Treatment Protocol

The patient populations on the pilot protocol and on the two clinical protocols did not differ significantly with regard to risk group, age, gender, WBC, platelets, hematocrit, liver size, or percentage of T-lineage ALL cases. Patients enrolled in protocol 91-01 had less splenomegaly and were less likely to be Hispanic than those in the other two studies. Fewer patients in protocol 87-01 had CNS disease at diagnosis compared with the other two studies. These differences in patient populations are not likely to be clinically significant with respect to the risk of infectious complications during remission induction.

There was no significant difference in the toxic induction death rate, the rate of failure due to refractory disease, or the remission induction rate between protocols 87-01 and 91-01 (Table 4; $P = 0.21$, $P = 0.29$, and $P = 0.11$, respectively). Nine of the 369 patients treated on protocol 87-01 did not achieve remission due to refractory leukemia, and 4 others died during remission induction therapy (remission induction rate = 96.5%). The four induction deaths were all related to sepsis. Similarly, of the 377 children treated on the protocol 91-01, 5 had persistent leukemia, and 1 other died of multisystem organ failure precipitated by *Pseudomonas* sepsis (remission induction rate = 98.4%).

Remission induction outcomes of patients treated on the pilot protocol were significantly worse than those of patients treated on the two clinical protocols (Table 4). The overall remission induction rate of protocol 91-01P was 89% (34 of 38 patients), with all induction failures caused by septic deaths. There was statistically no difference between protocol 91-01P and protocols 87-01 or 91-01 with regard to the frequency of induction failures from refractory disease. The toxic death rates found on protocols 87-01 and 91-01, however, differed substantially compared with protocol 91-01P ($P = 0.0035$ and $P = 0.0003$, respectively). Predictably, the overall remission induction rate for the pilot study was lower than that for either protocol 87-01 ($P = 0.06$) or protocol 91-01 ($P = 0.008$).

The overall 5-year EFS of protocol 91-01P was 66% $\pm$ 8%; 7 patients have relapsed, and 2 died in remission. However, no significant difference in LFS was found between protocols 91-01P and 91-01 ($P = 0.43$) or between protocols 91-01P and 87-01 ($P = 0.98$).

DISCUSSION

Four septic deaths (10.5% of patients) and potentially life-threatening sepsis in 12 other children (31.6% of patients) occurred during induction treatment on protocol 91-01P. This compared with a significantly lower total incidence of $\leq$1% toxic induction deaths on the preceding protocol 87-01 and subsequent protocol 91-01 treatment regimens for childhood ALL. No changes in supportive care measures, antibiotic use, or central venous line care policies were instituted that could explain this discrepancy. The only major difference between these three remission induction therapies was the substitution of dexamethasone for prednisone at equipotent systemic doses in the pilot protocol (Table 1).

Dexamethasone has theoretic advantages compared with prednisone, including an increased half-life and a prolonged duration of action. Thus, dexamethasone results in higher trough levels and higher steady-state concentrations.[4] Furthermore, binding to cortisol-binding globulin in plasma is lower for dexamethasone than for other glucocorticoids, which results in a higher fraction of plasma dexamethasone available to tissue and to lymphoblasts.[4,17] Finally, the decreased protein binding allows for greater cerebrospinal fluid penetration, which results in a lower incidence of CNS leukemia.[17,18,22]

However, we demonstrated that the toxicity associated with dexamethasone used during induction therapy outweighed its potential benefits. Only 89% of children treated on protocol 91-01P achieved a complete remission, which compared poorly with results obtained on current DFCI protocols as well as most other modern clinical induction regimens.[23–26] All induction failures were due to infectious deaths. Sixteen distinct episodes of documented sepsis and 1 episode

of documented fungal pneumonia during induction occurred in a total of 16 of the 38 children (42%) treated on protocol 91-01P. Episodes of sepsis were not captured in protocols 87-01 and 91-01 prospectively unless the events resulted in death. However, a retrospective review of 72 children treated on DFCI protocol 85-01 found only 14 episodes of documented sepsis (19%) during induction.[27] None of those episodes resulted in death. Four children treated with the 91-01P induction regimen, however, died from complications of their sepsis despite early treatment with broad-spectrum antibiotics. Thus, while not conclusive, the use of dexamethasone in protocol 91-01P may have increased the risk of infection and irreversible septic shock. It is unclear why dexamethasone may raise the incidence of infectious complications in ALL induction therapy. Unfortunately, possible explanations, such as differences in duration of neutropenia, qualitative differences in patients' bone marrow cellularity at the end of induction, or differences among quantitative immunoglobulin levels, were not captured on patients in any of the three studies.

Other investigators have substituted dexamethasone for prednisone during remission induction.[16,18,22] In the early 1970s, Jones et al. randomized children with ALL to receive prednisone or dexamethasone during induction and maintenance[18] and reported a remission induction rate similar to that of protocol 91-01P (85.7%); however, that trial was conducted prior to the knowledge of risk classification, utilized intravenous asparaginase (which likely led to several severe toxic reactions),[28] and included no CNS treatment during induction. The toxic death rates in the prednisone-treated versus the dexamethasone-treated patients were not reported.

More recently, the Children's Cancer Group (CCG) reported preliminary results showing an improved 3-year EFS in children with lower risk ALL treated with dexamethasone during induction and maintenance (EFS 91% $\pm$ 1%) compared with children treated with prednisone (EFS 86% $\pm$ 2%, $P = 0.01$).[22] Preliminary results of the DFCI protocol 91-01, which included dexamethasone during postremission therapy (but not during induction), also demonstrated a superior outcome with an overall 4-year EFS of 84% $\pm$ 4%.[19] Conversely, patients treated on protocol 91-01P, which had the same post-remission therapy as that delivered on protocol 91-01, had a vastly inferior overall EFS (66% $\pm$ 8%), due primarily to an increased number of toxic deaths during induction. Notably, LFS did not differ between protocols 91-01P and 91-01 or 87-01 ($P = 0.43$ and 0.98, respectively). Thus, the poor results of protocol 91-01P were likely due to the substitution of dexamethasone in an otherwise intensive four- to five-drug remission induction regimen that is standard in DFCI childhood ALL protocols.

The Dutch ALL investigators also reported results of their Study VI, which introduced dexamethasone in place of prednisone during induction and maintenance therapy.[16] Nonfatal toxicities commonly attributed to glucocorticoids, including weight gain, sleep disorders, and character disturbances, appeared more pronounced in Study VI compared with the preceding protocol, which used prednisone. However, despite 4 weeks of dexamethasone at identical doses used in protocol 91-01P, only 1 septic death was reported among 190 patients studied with an overall remission induction rate of 96.8%.

Differences between the administered therapy on the Dutch and the DFCI protocols may explain the widely different results. The Dutch regimen used a 2-drug induction (vincristine and dexamethasone) for the first 4 weeks of therapy (followed by 14 daily asparaginase injections as a third drug during the fifth and sixth week) compared with the 4- to 5-drug induction regimen used in DFCI protocols (Table 1). The negligible toxicity observed in the Dutch study relative to the toxicity observed in protocol 91-01P suggests that dexamethasone can be safely used in a moderately nonmyelosuppressive induction regimen. This potent steroid, however, appears to increase the risk of infectious episodes when incorporated into a more intensive, multiagent regimen.

Although several contemporary pediatric ALL trials, including the preliminary results of the DFCI 91-01 study, advocate the use of dexamethasone over prednisone during intensification and continuation as well as in induction,[16,19,22] we found that the simple substitution of dexamethasone in an intensive, multiagent induction regimen resulted in an intolerable number of infectious episodes and necessitated the early termination of the pilot protocol. In the subsequent protocol, we changed the glucocorticoid back to prednisone, and deleted the single dose of asparaginase (Table 2). These modifications yielded a remission induction rate of 98.3%, with only 1 septic death in 377 enrolled patients. It is doubtful that the asparaginase contributed to the high rate of sepsis. A single injection of high dose asparaginase in the preceding protocols 85-01[29] and 87-01 did not compromise the remission induction rate or result in a high number of septic episodes or toxic deaths. Caution should therefore be used against the routine substitution of dexamethasone in intensive ALL induction regimens. Awareness of this potentially fatal complication, and intensive supportive care of children with newly diagnosed ALL who do receive dexamethasone during induction, may optimize outcome.

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