Published in final edited form as:

Lancet Oncol. 2010 November ; 11(11): 1096–1106. doi:10.1016/S1470-2045(10)70114-5.

Glucocorticoid use in acute lymphoblastic leukemia: comparison of prednisone and dexamethasone

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Abstract

Glucocorticoids (prednisone and dexamethasone) play an essential role in the treatment of acute lymphoblastic leukemia (ALL) but their optimal doses and bioequivalence have not been established. Pre-clinical studies showed that dexamethasone has a longer half-life and better central nervous system (CNS) penetration. In prospective randomized trials, dexamethasone yielded better control of CNS leukemia. At a prednisone (mg)/dexamethasone (mg) dose ratio less than 7, dexamethasone treatment (6–18 mg/m²/day) yielded event-free survival superior to that of prednisone (40–120 mg/m²/day), and high-dose dexamethasone (10–18 mg/m²/day) overcame drug resistance in T-ALL and high-risk ALL. However, dexamethasone caused more adverse effects, including infection, bone fracture, osteonecrosis, mood and behavior problems, and myopathy. In studies using a dose ratio greater than 7, the two drugs showed no difference in efficacy. Therefore, the relative efficacy of prednisone and dexamethasone is dose dependent and must be carefully weighed against toxicity. Moreover, although dexamethasone generally exhibited greater activity against ALL cells in vitro, the dose ratio of the two drugs that exerted equivalent cytotoxicity ranged widely among individual samples. Selection of the type and dosage of glucocorticoid should be based on the risk of relapse, the treatment phase, and the concomitant chemotherapeutic drugs.

Keywords

glucocorticoid; dexamethasone; prednisone; acute lymphoblastic leukemia

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The authors have no conflicts of interest, including specific financial interests, relationships, or affiliations relevant to the subject of this manuscript.

Authors' contributions

HI performed the literature search and selected the relevant publications. Both authors were responsible for conception and design of the review, manuscript writing and revision, and final approval of the manuscript.

Search strategy and selection criteria

We searched Medline and PubMed for articles published in English during or after 1950, using the search terms "acute lymphoblastic leukemia," "glucocorticoid," "prednisone," "prednisolone," and "dexamethasone." Additional information was obtained from abstracts presented at the American Society of Hematology annual meeting.

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Introduction

Glucocorticoids were among the first drugs used in the treatment of acute lymphoblastic leukemia (ALL) and have remained essential components of therapy.^{1, 2} Their cytotoxic effect appears to be mediated through the binding of glucocorticoid receptors (figure 1).³ After binding to glucocorticoids in the cytoplasm, glucocorticoid receptors can homodimerize, translocate to the nucleus, and interact with glucocorticoid response elements to transactivate gene expression, or they can remain monomeric and repress the activity of transcription factors such as activating protein-1 (AP-1) or nuclear factor- κ B (NF- κ B).⁴⁻⁶ Both processes inhibit cytokine production,⁷ alter the expression of various oncogenes,⁸ and induce cell cycle arrest⁹ and apoptosis.¹⁰

In vivo and *in vitro* glucocorticoid resistance is an adverse prognostic factor in ALL, and several mechanisms have been reported.¹ Glucocorticoid exposure induces up-regulation of the glucocorticoid receptor in ALL cells and approximately half of the 51 responsive genes identified have been functionally linked to 3 major pathways: cell proliferation and survival (MAPK pathways), NF- κ B signaling and glucose metabolism.^{11, 12} Glucocorticoid resistance has been associated with up-regulation of genes involved in glucose metabolism and increased glucose consumption.^{11, 13, 14} Glucocorticoids also release Ca^{2+} from the endoplasmic reticulum into the cytosol; the resulting mitochondrial Ca^{2+} increase induces cytochrome c release and triggers apoptosis. Elevated expression of calcium-binding proteins S100A8 and S100A9 and of the anti-apoptotic BCL-2 protein family member MCL-1 inhibited free cytosolic Ca^{2+} and mitochondrial Ca^{2+} signals, respectively, causing glucocorticoid resistance.¹⁵⁻¹⁷

Traditionally, prednisone has been the glucocorticoid most commonly used in ALL therapy; it is typically given for 4 consecutive weeks in combination with vincristine, an anthracycline, asparaginase, and intrathecal chemotherapy. Dexamethasone, another glucocorticoid, is used increasingly in recent years to treat ALL. These two glucocorticoids are synthetic analogs of cortisol that differ molecularly in several important aspects (figure 2).¹⁸⁻²¹ Dexamethasone differs from prednisolone (active metabolite of prednisone) only by a fluorine atom in the 9 α position of ring B and a methyl group in the C 16 position of ring D. The 9 α fluorine slows the metabolism of dexamethasone, thereby extending its plasma half-life (200 min vs. 60 min for prednisolone) and biological half-life (36–54 h vs. 24–36 h).^{19, 21} The C 16 methyl group minimizes dexamethasone's sodium-retention effect. Prednisone is considered to have half the mineral corticoid activity of cortisol, while dexamethasone is thought to have little or none.²¹

Bioequivalence studies of dexamethasone and prednisone have often yielded discordant results. Generally, 1 mg of dexamethasone has been considered equivalent to 5 to 10 mg of prednisone in reducing inflammation.²⁰⁻²² However, this assumption has not been experimentally confirmed. Here we review the use of prednisone and dexamethasone in ALL, weighing evidence from *in vitro* studies, preclinical models, and clinical studies; compare the drugs' benefits and adverse effects; and discuss their optimal uses.

In vitro cytotoxicity of prednisolone and dexamethasone

The cytotoxicity of prednisolone and dexamethasone to ALL cells was initially compared in samples from 133 pediatric patients with untreated ALL by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay in cell suspension cultures.²³ The cytotoxicity of dexamethasone was considerably greater than that of prednisolone and was much greater than that predicted by the relative anti-inflammatory effects of the drugs. The median LC₅₀ (concentration producing 50% cytotoxicity) values of prednisolone and dexamethasone were 3.5 μM and 0.2 μM , respectively, and the median ratio of the

prednisolone and dexamethasone LC₅₀ values was 16.2. Interestingly, the ratio ranged widely (from 0.7 to >500) in samples from individual patients.

Ito et al.²⁴ compared the in vitro cytotoxicity of prednisolone and dexamethasone in leukemia cells grown on bone marrow–derived stromal layers. The stromal cells create a microenvironment similar to that of bone marrow in vivo, preventing apoptosis of leukemic lymphoblasts and allowing their proliferation.²⁵ In 28 B-lineage ALL samples tested, prednisolone and dexamethasone had median LC₅₀ values of 43.5 nM and 7.5 nM, respectively. The median dexamethasone-to-prednisolone ratio was 1:5.5 for both the LC₅₀ and LC₉₀ values. This ratio was considerably lower than that determined by the MTT assay but was similar to the ratio of the drugs' estimated anti-inflammatory activity and to their conventional dose ratio. Again, individual samples showed a wide range in the dexamethasone-to-prednisolone LC₅₀ (1:1.0 to 1:24.4) and LC₉₀ (1:1.1 to 1:25.5) ratios.

It is not clear why dexamethasone is more cytotoxic to leukemia cells than prednisolone. Lippman et al.²⁶ identified a highly specific glucocorticoid receptor in preparations of cytosol from glucocorticoid-sensitive ALL cells. Several studies showed that the dexamethasone receptor complex is more stable than the prednisolone receptor complex²⁷ and that the glucocorticoid receptor of leukemia cells has greater affinity for dexamethasone than for prednisolone.^{26, 28} However, other studies showed that glucocorticoid receptor has similar affinity for prednisolone and dexamethasone.¹⁸ In addition, both in vitro cytotoxicity studies described above found a broad range in the dexamethasone-to-prednisolone LC₅₀ and LC₉₀ ratios in ALL cells from different patients.^{23, 24} These findings may reflect a difference between individual patients in their leukemic-cell prednisolone and dexamethasone receptor affinity or post-receptor signaling. Elucidation of the mechanism that determines the relative cytotoxicity of the two drugs would facilitate the selection of glucocorticoids for individual patients.

Central nervous system (CNS) penetration of glucocorticoids

The success of ALL treatment depends on effective CNS-directed therapy, and with the reduced use and eventual elimination of prophylactic cranial irradiation, glucocorticoids play an increasingly important role in CNS leukemia control in contemporary treatment protocols.²⁹ Glucocorticoids have been used to treat a variety of neurological disorders, such as cerebral edema, hemorrhage, meningitis, and epilepsy.³⁰ Dexamethasone is preferred for these conditions because of its long half-life, excellent CNS penetration, and anti-inflammatory properties. For the same reasons, dexamethasone is increasingly used in the treatment of ALL.

Balis et al.³¹ compared the disposition of prednisolone (40 mg/m²) and dexamethasone (6 mg/m²) (prednisolone/dexamethasone dose ratio, 6.67) in cerebrospinal fluid (CSF) after intravenous administration in a nonhuman primate model. Although peak CSF levels of the two steroids showed equivalent potency at this dose ratio, prednisolone had a shorter CSF half-life (2.9 vs. 4.1 hours), resulting in a CSF-to-plasma ratio of the area under the concentration-time curve lower than that of dexamethasone (0.08 vs. 0.15). The more rapid clearance of prednisolone from the CSF is likely to reflect a difference in the two drugs' plasma protein binding characteristics.³¹ Although dexamethasone was 70% protein-bound over a wide concentration range, the protein binding of prednisolone was concentration-dependent (from 60% at 10 μ M to 95% at 0.5 μ M and below). Therefore, the free plasma prednisolone concentration, which is in equilibrium with CSF concentration, decreases at a much more rapid rate. The shorter half-life of prednisolone in the CSF may limit the duration of leukemic-cell exposure to cytotoxic concentrations. Further, plasma prednisolone concentration after oral administration of 40 mg/m² prednisone was variable,

with peak levels in the 1- to 2- μ M range,³² at which more than 90% of plasma prednisolone would be protein-bound.³¹ Therefore, at the plasma concentrations achieved after standard oral doses of prednisone and dexamethasone, the different proportions of the two drugs that exists in the free plasma form is likely to produce a much greater difference in CNS exposure to an effective CSF drug concentration. The authors estimated that the CSF exposure achieved by prednisone would be only 10% to 20% of that achieved by dexamethasone.³¹ This study led to clinical trials in which the effects of prednisone (prednisolone) and dexamethasone were compared by randomization or were compared with historical data.

Early clinical trials

Early clinical trials (table 1) used the prednisone (prednisolone)/dexamethasone dose ratio (6.67) tested in a nonhuman primate model.³¹ In 1971, the first randomized trial in 493 children with ALL was performed by Cancer and Leukemia Group B (CALGB; table 1).³³ Patients received either 40 mg/m²/day of prednisone or 6 mg/m²/day of dexamethasone during remission-induction and maintenance therapy. Dexamethasone significantly reduced the frequency of CNS relapse (14.3% in 231 children treated with dexamethasone vs. 25.6% in 262 children treated with prednisone, $p=0.017$).

Subsequently, the Dutch Childhood Leukemia Study Group (DCLSG), the Dana-Farber Cancer Institute (DFCI) ALL consortium, and the St. Jude Total Therapy studies compared the results of dexamethasone treatment to those of historical controls treated with prednisone (table 1). Several treatment modifications in successive clinical trials precluded definitive conclusions, but nonetheless dexamethasone appeared to improve outcome. In the DCLSG ALL VI study, 190 children with non-high-risk ALL were given 6 mg/m²/day of dexamethasone (vs. prednisone 40 mg/m²/day in ALL V [240 patients]) during remission-induction and maintenance therapy (table 1).³⁴ The treatment results of the DCLSG ALL VI study (8-year event-free survival, 81%; CNS relapse, 1.1%) compared favorably with those of the DCLSG ALL V (10-year event-free survival, 49% and 56%, depending on the use of rubidomycin; CNS relapse, 12.9%).

In DFCI ALL Consortium Protocol 91-01(377 patients), postremission therapy was intensified by substituting dexamethasone (6 mg/m²/day for standard-risk and 18 mg/m²/day for high-risk groups) for prednisone and by prolonging the asparaginase intensification phase from 20 to 30 weeks (table 1).³⁵ The 5-year event-free survival estimate was 83% and the 5-year CNS-leukemia-free survival estimate was 98% in standard-risk and 96% in high-risk patients, which was significantly better than the results of DFCI ALL Consortium protocols conducted between 1981 and 1991 ($p=0.03$). In the St. Jude Total Therapy XIII A study (165 patients), 22% received prophylactic cranial irradiation; the 5-year event-free survival estimate was 77.6%, and the cumulative risk of isolated CNS relapse was 1.2%.³⁶ In the subsequent Total XIII B study (247 patients), prednisone was replaced by dexamethasone for postremission therapy and prophylactic cranial irradiation was limited to 12% of patients, resulting in a 5-year event-free survival estimate of 80.8% and a 1.7% cumulative risk of isolated CNS relapse.³⁷ Despite the use of historical comparisons, these studies suggested that dexamethasone provided improved event-free survival and CNS control even when used after remission-induction therapy.

Randomized clinical trials using different prednisone/dexamethasone ratios

The DFCI 91-01 protocol included a 3-day window-therapy phase in which 369 pediatric ALL patients were randomly assigned to receive prednisolone 40 mg/m²/day or

dexamethasone 6, 18, or 150 mg/m²/day before remission-induction therapy (table 1).^{35, 38} The dose of dexamethasone was positively associated with the degree of bone marrow response (p=0.007). Higher-dose dexamethasone treatment abrogated the effect of relative drug insensitivity and of low glucocorticoid receptor expression on leukemia blast cells. Therefore, several randomized trials have investigated various prednisone/dexamethasone ratios by increasing the prednisone (40 to 120 mg/m²/day) or dexamethasone (6 to 18 mg/m²/day) doses.

Dexamethasone was superior to prednisone in preventing CNS relapse and increasing event-free survival when used at the presumed biologically equipotent dose (prednisone/dexamethasone ratio, 6 to 7) (table 1). The Children's Cancer Group (CCG)-1922 study randomized 1060 patients at standard risk by National Cancer Institute (NCI) criteria to receive prednisone (40 mg/m²/day) or dexamethasone (6 mg/m²/day) during remission-induction, consolidation, and maintenance therapy (prednisone/dexamethasone ratio=6.67; table 1).³⁹ Patients assigned to the dexamethasone arm had a lower 6-year incidence of isolated CNS relapse (3.7% vs. 7.1%; p=0.01) and a higher event-free survival estimate (85% vs. 77%; p=0.002). Similarly, the Medical Research Council (MRC) ALL 97/99 study randomized 1603 children with standard- and high-risk ALL (table 1).⁴⁰ Patients who received dexamethasone (6.5 mg/m²/day) rather than prednisolone (40 mg/m²/day) (prednisolone/dexamethasone ratio=6.15) during the induction, consolidation, and continuation phases had half the risk of isolated CNS relapse (2.5% vs. 5%; p=0.0007). Five-year event-free survival was significantly greater with dexamethasone (84.2% vs. 75.6%; p=0.007). Randomization in this study was closed early because of the observed superiority of dexamethasone.

Dexamethasone was also associated with a higher event-free survival estimate even when it was used only after induction therapy. In the recently reported DFCI 00-01 protocol, 408 patients were randomized to receive a 5-day course of either prednisone or dexamethasone every 3 weeks during intensification and continuation therapy, after prednisone-based remission-induction therapy (table 1).⁴¹ The standard-risk patients received prednisone 40 mg/m²/day and dexamethasone 6 mg/m²/day, and the high-risk group received higher doses (prednisone 120 mg/m²/day and dexamethasone 18 mg/m²/day) during intensification therapy (prednisone/dexamethasone ratio=6.67). The 5-year event-free survival estimate was 90% in the dexamethasone arm and 81% in the prednisone arm (p=0.01). The benefit of dexamethasone was more evident among patients with high-risk ALL (5-year event-free survival, 91% vs. 78%) than among standard-risk patients (89% vs. 84%). The higher dose of dexamethasone apparently overcame the adverse prognosis of the high-risk group.

After a 7-day prednisone prophase, higher doses of prednisone (60 mg/m²) and dexamethasone (10 mg/m²) (prednisone/dexamethasone ratio=6) during induction therapy were evaluated in 3655 patients in the ALL 2000 Berlin-Frankfurt-Münster/Associazione Italiana Ematologia Oncologia Pediatrica (BFM/AIEOP) study (table 1).⁴² Again, 6-year event-free survival was greater with dexamethasone than with prednisone (84.1% vs. 79.1%; p=0.0083). There was a significant difference in the 6-year cumulative risk of relapse (11% for dexamethasone vs. 18% for prednisone; p<0.001); the difference was observed for isolated bone marrow relapse (8% vs. 12%), CNS relapse (2% vs. 4%), and other relapse (2% vs. 3%). While the risk of relapse was reduced by dexamethasone in both T-cell ALL and B-cell precursor ALL, the reduction was most pronounced among patients with T-ALL (cumulative risk of relapse, 6% vs. 20%; p=0.003) and among those with *ETV6-RUNX1* (also known as *TEL-AML1*)–positive B-cell precursor ALL (4% vs. 13%; p<0.001) who had a good response to the prednisone prophase.

However, the relative merits of dexamethasone over prednisone may be dependent on the dose ratio. Two studies using a prednisolone/dexamethasone ratio greater than 7 disclosed no significant difference in event-free survival. The Tokyo Children's Cancer Study Group (TCCSG) L95-14 protocol randomly assigned 231 children with standard-risk ALL and 128 with intermediate-risk ALL to prednisolone 60 mg/m² or dexamethasone 8 mg/m² during remission-induction (prednisolone/dexamethasone ratio, 7.5; table 1).⁴³ Eight-year event-free survival was 84.4% in the prednisolone arm and 81.1% in the dexamethasone arm among standard-risk patients (p=0.22) and was 80.4% vs. 84.9%, respectively, in the intermediate-risk group (p=0.63). The event-free survival estimates in the prednisolone arm of this study appeared to be better than those observed in the CCG-1922 and MRC 97/99 trials, perhaps partly because of the higher prednisolone dosage (60 mg/m² vs. 40 mg/m²). There were 2 extramedullary relapses in the dexamethasone arm vs. 7 in the prednisolone arm. The European Organization for Research and Treatment of Cancer (EORTC) 58951 study (1703 patients) investigated a prednisolone/dexamethasone ratio of 10 (prednisolone 60 mg/m² and dexamethasone 6 mg/m²; table 1).⁴⁴ The study arms did not differ significantly in the complete remission rate (both 98.4%) or the 5-year event-free survival estimate (82.4% for prednisolone vs. 82.1% for dexamethasone, p=0.94), even when the results were analyzed separately for B-cell precursor ALL and T-cell ALL. The 5-year cumulative incidence of CNS relapse was 4.9% vs. 2.9%; of non-CNS relapse, 9.4% vs. 10.9%; and of death during complete remission, 2.1% vs. 2.7% in the prednisolone and dexamethasone arms. Hence, at these doses and ratios, prednisolone and dexamethasone had equivalent efficacy.

Comparison of adverse effects of prednisone and dexamethasone

Side effects of glucocorticoids vary depending on the dose and the duration of treatment. The relative toxicity of prednisone and dexamethasone has not been fully elucidated in patients with ALL, but toxicity has more often been associated with dexamethasone in published studies (table 1). Therefore, any benefits of dexamethasone must be weighed against the risk of toxicity and adverse effects.

Prolonged exposure to high-dose dexamethasone in conjunction with myelosuppressive therapy can cause severe infections during remission-induction therapy and requires meticulous supportive care. In the DFCI 91-01P protocol, 16 of the 38 children had documented sepsis (which was lethal to 4) when dexamethasone (6 mg/m²) was substituted for prednisone (40 mg/m²).⁴⁵ The incidence of death during induction was significantly greater than that in the previous protocol (DFCI 87-01; 1%, p=0.0035) and the subsequent protocol (DFCI 91-01; <1%, p=0.0003). In the ALL 2000 BFM/AIEOP study, the use of 10 mg/m² of dexamethasone was significantly associated with death during induction, caused largely by severe bacterial and fungal infections (table 1).⁴² The cumulative incidence of death during induction was 2% in the dexamethasone group and 0.9% in the prednisone group (p=0.003), and was especially high in patients ≥ 10 years of age (4.5% vs. 2.4%). This result prompted the study group to halt randomization for patients ≥ 10 years of age and assign all subsequent patients in this age group to receive prednisone. Recent analysis of the DFCI 00-01 protocol showed a significantly higher incidence of infection (positive blood culture or radiologic evidence of invasive fungal disease) among patients who received dexamethasone (18.8%) than among those who received prednisone (10.6%) (p=0.03), even though randomization was performed after remission-induction therapy (table 1).⁴¹

Bone toxicities such as fractures and osteonecrosis are associated with steroid therapy in ALL, especially in adolescent patients. Historical comparison of DFCI protocols (176 patients) showed that the 5-year cumulative incidence of bony morbidity, especially bone fracture, was significantly increased when dexamethasone was substituted for prednisone

(36% in DFCI 91-01 vs. 20% in DFCI 87-01, $p=0.04$; table 1).^{35, 46} Similarly, in the MRC 97/99 study, severe osteopenia was almost exclusively limited to patients receiving dexamethasone ($p<0.05$; table 1).⁴⁰ This toxicity was associated with stress fractures of the limbs or spine or with severe bone pain. The CCG reported an overall incidence of osteonecrosis of 14.2% in 893 patients ≥ 10 years of age versus 0.9% in 516 younger patients ($P<0.0001$).⁴⁷ Risk factors for osteonecrosis included the cumulative dose of dexamethasone, age ≥ 10 years, female sex, and white race/ethnicity. Similarly, the incidence of osteonecrosis among 1951 patients enrolled in the ALL-BFM 95 study was 8.9% in patients ≥ 10 years of age and 0.2% in younger patients ($p<0.01$).⁴⁸ Kadan-Lottick et al.⁴⁹ evaluated the incidence of osteonecrosis among 9261 long-term cancer survivors in the Childhood Cancer Survivor Study. Fifty-two survivors had osteonecrosis; their 20-year cumulative incidence of osteonecrosis was 0.43%, 6.2 times of that reported by siblings. The incidence was higher in survivors who had received dexamethasone with or without prednisone than in those who had received prednisone alone (relative risk 2.7, $p=0.019$). In the DFCI 00-01 study, the 5-year cumulative incidence of osteonecrosis was significantly higher with dexamethasone treatment (23% vs. 4.7% of those treated with prednisone, $p=0.02$) among patients 10–18 years of age, whereas no difference was seen among patients 1–10 years of age (table 1).⁴¹

Glucocorticoid treatment can affect mood and behavior, resulting in “steroid psychosis”.^{50, 51} Asthmatic children treated with prednisone showed a transient deficit in verbal memory, as did adult volunteers given a 4-day course of dexamethasone.^{52, 53} As dexamethasone has increased CNS penetration, its short- and long-term effects are of particular concern. In the MRC ALL 97/99 study, dexamethasone was associated with a significantly greater frequency of abnormal behavior (ranging from mood swings and lability to severe depression [more frequent in girls] and violence toward self or others [boys]) than was prednisolone (6% vs. 1%, $p<0.0001$; table 1).⁴⁰ In CCG-1922, dexamethasone-induced agitation was treated with concomitant potassium supplements and sedatives or a change to prednisone.³⁹ Although not studied systematically, potassium supplements appeared to benefit our patients, especially the younger ones, who received dexamethasone treatment. Reports of long-term effects are inconsistent. Historical comparison of the DFCI 87-01 and 91-01 protocols showed that post-remission dexamethasone may increase the risk of neurocognitive late effects.⁵⁴ Children who received dexamethasone on DFCI 91-01 performed poorly on 2 of the 4 measures of academic achievement (reading comprehension and arithmetic calculation), on a test of working memory, and on neuropsychological measures of learning disability (table 1). However, a cross-sectional study of children previously randomized to dexamethasone or prednisone in CCG-1922 showed no significant overall difference in neurocognitive and academic performance, except that patients who received dexamethasone scored approximately one-third of a standard deviation lower on a test of word reading.⁵⁵

Proximal myopathy is a complication of corticosteroid therapy.⁵⁶ In CCG-1922, the dexamethasone arm had a significantly greater prevalence of reversible grade 1–3 steroid myopathy (6.3% vs. 1.5% for prednisone, $p<0.0001$) and grade 3 weakness (4.1% vs. 0.3% for prednisone, $p<0.0001$) during or immediately after induction therapy (table 1).³⁹ Male sex and younger age were risk factors for development of severe weakness. In the MRC ALL 97/99 study, transient myopathy during induction therapy was 2.8% in the dexamethasone arm and 0.5% in the prednisolone arm ($p<0.001$; table 1).⁴⁰

It is difficult to compare the toxic effects of prednisone/prednisolone and dexamethasone in the absence of conclusive information about drug equivalency. Two studies found no significant difference in event-free survival between the prednisolone and dexamethasone arms. In the TCCSG L95-14 study, toxicity was not found to differ significantly but

complications were more prevalent in the dexamethasone arm (table 1).⁴³ In the EORTC 58951 study, patients treated with dexamethasone rather than prednisolone during remission-induction therapy experienced more frequent infection during consolidation therapy, particularly those randomized to receive prolonged asparaginase treatment during consolidation (table 1).⁴⁴

Future studies to optimize the use of glucocorticoids

The remarkable progress in the treatment of childhood ALL warrants a greater effort to reduce the morbidity and toxicity of glucocorticoid therapy without compromising its antileukemic benefit. Because the prednisolone/dexamethasone LC₅₀ and LC₉₀ ratios vary widely in vitro^{23, 24} and the activities of the two drugs differ in vivo, a clinical trial could reasonably use both prednisone and dexamethasone during the 2- to 3-year ALL treatment regimen unless sensitivity to either agent is clearly identified for the individual patients. The benefits of dexamethasone in CNS control and in treatment of T-ALL and high-risk ALL must be confirmed in protocol design. Future studies could seek to reduce glucocorticoid-associated complications during remission-induction therapy by reserving dexamethasone for post-induction therapy; during this phase, it was shown by DFCI and St. Jude studies to provide a significant benefit.^{35, 37, 41} When children with intermediate risk ALL were treated on BFM based protocols with intensive induction and reinduction therapies, pulses of dexamethasone and vincristine during continuation therapy added no benefit.⁵⁷ Future studies to reduce cumulative glucocorticoid exposure must precisely identify lower-risk patients and test agents and drug combinations that can replace glucocorticoids or alleviate glucocorticoid resistance. It would also be important to compare the acute and chronic glucocorticoid toxicities and quality of life among patients randomized to receive presumed clinically equivalent doses of prednisone and dexamethasone (dose ratio >7). Finally, research is needed to optimize supportive care to prevent and manage glucocorticoid toxicities.

The St. Jude Total XV (498 patients) and Dutch Childhood Oncology Group (DCOG) ALL-9 (859 patients) studies showed that prophylactic cranial irradiation can safely be eliminated from ALL treatment with the use of effective chemotherapy including dexamethasone.^{58, 59} The 5-year cumulative risk of isolated CNS relapse in these studies was 2.7% and 2.6%, respectively, which is within the range (1.5% to 4.5%) achieved in clinical trials that use prophylactic cranial irradiation. As multiple trials have shown its efficacy, dexamethasone will play an essential role in CNS-directed therapy in contemporary clinical trials (table 2).²⁹

Coustan-Smith et al.⁶⁰ recently identified a subset (12%–15%) of T-ALL characterized by the early T-cell precursor phenotype. These patients had a poor response to remission-induction treatment and a dismal outcome: the 10-year overall survival estimate of the 17 patients with this phenotype was 19%, in contrast to 84% for the other 122 patients with T-ALL ($P<0.0001$). Because of their high levels of minimal residual disease at the end of remission-induction, they are often offered hematopoietic stem cell transplantation during first remission and therefore would receive dexamethasone only if it were included in remission-induction therapy. The better results in T-ALL patients who received dexamethasone during remission-induction in the ALL 2000 BFM/AIEOP study would justify its early use in this group of patients (table 2).⁴² In the ongoing St. Jude Total XVI trial, we use high-dose dexamethasone during remission-induction (10 mg/m²/day) and post-remission therapy (12 mg/m²/day) for patients with this subtype of TALL.

Activating mutations of NOTCH1 are among the most common genetic abnormalities in T-ALL.⁶¹ As γ -secretase is required for NOTCH1 activation, inhibitors of this proteolytic step

might impede the function of oncogenic NOTCH1 and suppress T-ALL cell growth. However, clinical development of γ -secretase inhibitors has not been successful because of their limited antileukemic activity and severe gastrointestinal toxicity.^{62, 63} Real et al.⁶⁴ recently reported that a γ -secretase inhibitor was more effective and less toxic in an animal model of steroid-resistant TALL if used concomitantly with high-dose dexamethasone (table 2). This effect is mediated by transcriptional up-regulation of cyclin D2 and suppression of intestinal goblet cell metaplasia. Similarly, anti-apoptotic MCL-1 is an important regulator of glucocorticoid resistance,¹⁵ and Wei et al.¹⁶ showed that rapamycin induces dexamethasone sensitivity in malignant lymphoid cells by down-regulating this protein. Further, glucocorticoid resistance was associated with increased glucose consumption, and inhibition of glycolysis sensitized glucocorticoid-resistant ALL cells.¹³ Whether these findings can be translated into clinical use is uncertain.⁶⁵

Because leukemia patients have a limited bone marrow reserve of normal hematopoietic cells, careful attention is necessary to prevent serious or fatal infections (table 2). Prophylactic antibiotics and antifungal agents may be considered, especially if high-dose dexamethasone therapy is prolonged or combined with other cytotoxic chemotherapies. We recently reported that prophylactic treatment during intensive therapy for pediatric acute myeloid leukemia reduced infection and dramatically decreased the incidence of septicemia and the number of inpatient days.⁶⁶ We are now testing this strategy for ALL patients, especially during remission-induction and reinduction therapy. The absence of a surge in the granulocyte count after dexamethasone pulse therapy during continuation treatment signifies low bone marrow reserve and requires dose reduction or withholding of cytotoxic chemotherapy to prevent serious and fatal infection.^{59, 67} Hypogammaglobulinemia is also common during continuation therapy, and supplemental immunoglobulin therapy should be considered for patients who experience frequent infections.^{59, 68}

Given the high incidence of fracture and osteonecrosis in adolescents with ALL, future studies should investigate strategies to reduce these toxicities (table 2). Mattano et al.⁶⁹ observed a lower frequency of osteonecrosis in patients who received discontinuous dexamethasone (10 mg/m²/day on days 0–6 and 14–20) than in those who received continuous dexamethasone (10 mg/m²/day on days 0 through 20) during delayed intensification therapy, and several ongoing studies have incorporated this strategy to confirm the result. Bisphosphonates are another therapeutic option that might reduce the risk of pathologic fracture, as they reduce corticosteroid-induced osteoporosis in adults with nonmalignant conditions.⁷⁰ However, the safety and efficacy of bisphosphonates in pediatric ALL patients have yet to be determined. The receptor activator of NF- κ B ligand (RANKL), its cognate receptor RANK, and its natural decoy receptor osteoprotegerin have been identified as the final effector molecules of osteoclastic bone resorption. Therefore, a specific inhibitor of RANKL could be considered.⁷¹ Strict monitoring of energy intake and weight gain is essential to limit weight-bearing stress on the hip and knee joints.⁷² Obese patients, especially those receiving chronic steroid therapy, may benefit from interventions designed to increase their physical activity, optimize their nutrition, and modify obesity-associated behaviors. It would also be of interest to evaluate whether early and intensive screening for osteonecrosis by imaging studies would allow the prevention of significant functional impairment.⁷³

There is no consensus on when and how to modify the glucocorticoid dose or on when to discontinue glucocorticoids in patients with established glucocorticoid toxicity. Severe psychosis induced by dexamethasone can be managed by dose reduction or by switching to prednisone.³⁹ Our current Total XVI study assesses halving the dexamethasone dose for asymptomatic patients with magnetic resonance imaging findings of significant osteonecrosis and replacing dexamethasone with antimetabolites for patients with

symptomatic osteonecrosis, especially those who have completed second reinduction therapy.

Glucocorticoids are given in the context of combination chemotherapy that includes vincristine, daunorubicin, and asparaginase. Belgaumi et al.⁷⁴ described the higher incidence of toxicity when daunorubicin was added to dexamethasone-based, rather than prednisone-based, induction chemotherapy. During reinduction therapy in the St. Jude Total XV study, interpatient and inpatient dexamethasone apparent clearance varied by a factor greater than 10.⁷⁵ This variability was explained by patients' serum albumin concentration, age, concomitant fentanyl and ketoconazole use, and the treatment arms that featured different intensity of asparaginase treatment. Hypoalbuminemia, a well-recognized effect of asparaginase treatment that may reflect impaired hepatic function, was associated with lower clearance of dexamethasone. Steroid-induced adverse effects are more likely to develop in children older than 10 years, who have a slower rate of dexamethasone clearance than younger patients.⁷⁵ Hence, treatment- and host-related factors greatly affect systemic exposure to glucocorticoids and may explain the variable responses and toxicities (table 2). Ongoing genome-wide studies of host pharmacogenetics and leukemic cell genetic abnormalities may help to optimize the use of glucocorticoids in ALL therapy. Ideally, such studies would identify genetic mutations and/or polymorphisms that can differentiate the likelihood of leukemia response from the risk of toxicity induced by glucocorticoids, allowing early therapeutic interventions.

Conclusion

Dexamethasone reduces the frequency of CNS relapse and is more effective than prednisone at a prednisone/dexamethasone dose ratio below 7. When the prednisone/dexamethasone dose ratio is greater than 7, event-free survival estimates are comparable with the two drugs, although dexamethasone still appears to yield better CNS control. A high dose (e.g., dexamethasone at 10 to 18 mg/m²/day) can overcome drug resistance in T-cell ALL and high-risk ALL. The toxicities associated with prednisone treatment are generally less than those with dexamethasone treatment.

In view of its better CNS penetration and possibly greater efficacy against T-cell ALL, dexamethasone may be particularly useful for patients with this ALL subtype. Because the relative sensitivity of ALL cells to dexamethasone and prednisone varies among individual patients and the toxicities of glucocorticoids differ according to concomitant chemotherapy used, it may be reasonable to use both prednisone and dexamethasone in the treatment of ALL. Future studies are needed to determine the preferred glucocorticoid for specific phases of treatment and the optimal duration and dose.

Acknowledgments

We acknowledge the expertise of Sharon Naron, ELS, in editorial review of the manuscript.

Supported in part by Cancer Center Support Grant CA21765 from the National Institutes of Health and by the American Lebanese Syrian Associated Charities (ALSAC). Dr. Pui is an American Cancer Society Professor.

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Figure 1. Glucocorticoid receptor signaling

Extracellular glucocorticoid released from circulating steroid-binding protein (SBP) enters the cell by passive transport due to its relatively small size and lipophilicity. The unbound glucocorticoid receptor (GR) forms heterocomplexes with chaperone heat shock proteins (hsp) 90 and 70 and co-chaperone immunophilin FK506 binding protein (FKBP) 52, which are required for optimal binding of glucocorticoid. After binding, the GR dissociates from its (co-) chaperone proteins, unmasking the GR domain responsible for nuclear translocation. GRs can homodimerize and interact with glucocorticoid response elements (GRE) to induce gene transcription (transactivation) or they can remain monomers and interact with transcription factors such as activating protein-1 (AP-1) or nuclear factor-κB (NF-κB) (transrepression). Both mechanisms produce clinically observed effects of glucocorticoids.

Figure 2.
Chemical structures of cortisol and of the synthetic glucocorticoids prednisone, prednisolone, and dexamethasone.

Table 1

Studies comparing prednisone (prednisolone) and dexamethasone

Study	Patients	Steroid (mg/m ² /day)	Pred/Dex ratio	Results (pred vs. dex)	Adverse effects (pred vs. dex)
CALGB ³³	493 patients	Pred 40 vs. dex 6 Induction and maintenance	6.67	CNS relapse 25.6% vs. 14.3% (p=0.017) BM relapse and OS (NS)	NA
DCLSG ALL VI ³⁴	190 non-HR	Dex 6 vs. pred 40 in previous protocol Induction and maintenance	6.67	8-y EFS 81% (vs. 10-y EFS 49% and 56% in ALL V) CNS relapse 1.1% (12.9% in ALL V)*	More obesity, sleep disorder, and character disturbance with dex*
DFCI 91-01 ³⁵	377, SR and HR	Dex 6 (SR) and 18 (HR) vs. pred 40 (SR) and 120 (HR) in prior protocols Intensification and maintenance	6.67	5-y EFS 83% (p=0.03)** CNS relapse 2% (SR) and 4% (HR)	Bone fracture 20% vs. 36% (p=0.04) ^{#46} More neurocognitive sequelae with dex ^{#54}
DFCI 91-01 ^{35, 38}	369, SR and HR	Pred 40 and dex 6, 18, and 150 Window therapy	6.67, 2.22, and 0.27	Day 3 BM response: 19%, 29%, 48%, 50%, respectively (p=0.007)	NA
CCG-1922 ³⁹	1060, SR	Pred 40 vs. dex 6 Induction, consolidation and maintenance	6.67	6-y EFS: 77% vs. 85% (p=0.002) 6-y OS: 91% vs. 93% (NS) CNS relapse: 7.1% vs. 3.7% (p=0.01) BM relapse: 11.1% vs. 7.9% (NS)	Myopathy 1.5% vs. 6.3% (p<0.0001) Weakness 0.3% vs. 4.1% (p<0.0001) Hyperglycemia 1.5% vs. 5% (p=0.001) Long term cognitive function (NS) ⁵⁵
MRC ALL 97/99 ⁴⁰	1603, SR and HR	Pred 40 vs. Dex 6.5 Induction, consolidation, and continuation	6.15	5-y EFS: 75.6% vs. 84.2% (p=0.0007) 5-y OS: 85.8% vs. 89.0% (NS) CNS relapse: 5.0% vs. 2.5% (p=0.007)	Osteopenia 0.1% vs. 0.9% (p<0.05) Behavioral problems 1% vs. 6% (p<0.0001) Myopathy 0.5% vs. 2.8% (p<0.001) Randomization discontinued early
DFCI 00-01 ⁴¹	408, SR and HR	Pred 40 vs. Dex 6 Intensification (SR) and continuation (SR and HR) Pred 120 vs. Dex 18 Intensification (HR)	6.67	5-y EFS: 81% vs. 90% (p=0.01) SR: 84% vs. 89% HR: 78% vs. 91%	Osteonecrosis within 10–18 y: 4.7% vs. 23% (p=0.02) Infection: 10.6% vs. 18.8% (p=0.03)
ALL 2000 BFM/AIEOP ⁴²	3655 patients	Pred 60 vs. Dex 10 Induction	6.0	6-y EFS: 79.1% vs. 84.1% (p=0.0083) 6-y relapse rate: 18% vs. 11% (p<0.001) CNS relapse: 4% vs. 2% BM relapse: 12% vs. 8% Relapse in T-ALL: 20% vs. 6% (p=0.003) Relapse in TEL-AML1/B-ALL: 13% vs. 4% (p<0.001)	Death during induction: 0.9% vs. 2% (p=0.003) High frequency of severe bacterial and fungal infection with dex Randomization discontinued for patients ≥10 y.o.
TCCSG L95-14 ⁴³	231 SR and 128 IR	Pred 60 vs. Dex 8 Induction	7.5	SR 8-y EFS: 84.4% vs. 81.1% (NS) IR 8-y EFS: 80.4% vs. 84.9% (NS)	More prevalent in dex
EORTC 58951 ⁴⁴	1703 patients	Pred 60 vs. Dex 6	10	5-y EFS: 82.4% vs. 82.1% (NS) CNS relapse: 4.9% vs. 2.9%	Infection during consolidation: 21.1% vs. 23.5%

Study	Patients	Steroid (mg/m ² /day)	Pred/Dex ratio	Results (pred vs. dex)	Adverse effects (pred vs. dex)
		Induction and continuation		Non-CNS relapse: 9.4% vs. 10.9%	(with prolonged L-Asp: 21.8% vs. 29.1%)

* Historical comparison with previous study

** Historical comparison with previous 3 protocols

Abbreviations: Pred: prednisone/prednisolone, Dex: dexamethasone, CALGB: Cancer and Leukemia Group B, DCLSG: Dutch Childhood Leukemia Study Group, ALL: acute lymphoblastic leukemia, DFCl: Dana-Farber Cancer Institute, CCG: Children's Cancer Group, MRC: Medical Research Council, BFM/AIEOP: Berlin-Frankfurt-Münster/Associazione Italiana Ematologia Oncologia Pediatrica, TCCSG: Tokyo Children's Cancer Study Group, EORTC: European Organization for Research and Treatment of Cancer, HR: high risk, SR: standard risk, IR: intermediate risk, CNS: central nervous system, BM: bone marrow, NS: not significant, EFS: event free survival, OS: overall survival, NA: not available

Table 2**Future studies of glucocorticoid treatment in acute lymphoblastic leukemia****Possible benefits of dexamethasone use**

- Central nervous system leukemia prevention and control
- T-cell leukemia
- Co-administration with NOTCH 1 inhibitor, rapamycin, or glycolysis inhibitor

Evaluation and optimization of drug exposure

- Dexamethasone short-term pulse therapy
- Pharmacokinetics
- Pharmacogenetics

Prevention of infection

- Prophylactic antibiotics and antifungal agents during profound bone marrow suppression
- Monitoring of granulocyte surge after dexamethasone use
- Immunoglobulin supplementation

Prevention of bone sequelae (fractures and osteonecrosis)

- Monitoring of energy intake and weight gain
- Physical activity interventions, nutritional guidance, and behavioral modification
- Early and intensive screening by imaging and intervention
- Bisphosphonates
- Inhibitor of receptor activator of nuclear factor- κ B ligand (RANKL)

Management of steroid psychosis

- Psychology support
- Sedatives
- Potassium supplementation