Published in final edited form as:

Pediatr Blood Cancer. 2013 November ; 60(11): 1785–1791. doi:10.1002/pbc.24666.

Neuropsychological Outcomes of a Randomized Trial of Prednisone Versus Dexamethasone in Acute Lymphoblastic Leukemia: Findings From Dana-Farber Cancer Institute ALL Consortium Protocol 00-01

Deborah P. Waber, PhD^{1,2,*}, Marie McCabe, PhD¹, Mikaela Seabee, PhD^{1,3}, Peter W. Forbes, MS⁴, Heather Adams, PhD⁵, Cheryl Alyman, PhD, CPsych⁶, Stephen A. Sands, PsyD⁷, Philippe Robaey, MD, PhD^{8,9}, Ivonne Romero, PhD¹⁰, Marie-Ève Routhier, DPsy¹¹, Jonathan M. Girard, BA¹, Stephen E. Sallan, MD¹², and Lewis B. Silverman, MD¹²

¹Division of Psychology, Department of Psychiatry, Boston Children's Hospital, Boston, Massachusetts

²Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

³St. Luke's Children's Hospital, Boise, Idaho

⁴Clinical Research Center, Boston Children's Hospital, Boston, Massachusetts

⁵Division of Child Neurology, Department of Neurology, University of Rochester Medical Center, Hamilton, Ontario, Canada

⁶Division of Pediatric Hematology/Oncology, McMaster University, Hamilton, Ontario, Canada

⁷Department of Psychiatry, Columbia University Medical Center, Montreal, Quebec, Canada

⁸Department of Psychiatry, University of Montreal, Montreal, Quebec, Canada

⁹Department of Psychiatry, University of Ottawa, San Germán, Puerto Rico

¹⁰Interamerican University, San Germán, Puerto Rico

¹¹Division of Psychology, Department of Pediatric Hematology/Oncology, Centre Mère-Enfant, Montreal, Quebec, Canada

¹²Division of Hematology and Oncology, Department of Medicine, Boston Children's Hospital and Department of Pediatric Oncology, Dana Farber Cancer Institute, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

Abstract

Background—Dexamethasone is more efficacious than prednisone in the treatment of acute lymphoblastic leukemia (ALL), but has also been associated with greater toxicity. We compared neuropsychological outcomes for patients treated on DFCI ALL Consortium Protocol 00-01,

*Correspondence to: Deborah P. Waber, Department of Psychiatry, Boston Children's Hospital, Pavilion 155 300 Longwood Avenue, Boston, MA 02115. deborah.waber@childrens.harvard.edu.

Conflict of interest: Nothing to disclose.

which included a randomized comparison of the two steroid preparations during post-induction therapy in children and adolescents with ALL.

Procedure—Between 2000 and 2005, 408 children with standard-risk or high-risk ALL treated on Dana-Farber Cancer Institute Consortium Protocol 00-01 were randomly assigned to prednisone or dexamethasone administered as 5-day pulses every 3 weeks for 2 years, beginning at week 7 of treatment. Blinded neuropsychological testing was completed for 170 randomized patients (prednisone, N = 76; dexamethasone, N = 94), all of whom were in continuous complete remission after completion of therapy.

Results—Outcomes were comparable for most variables, although patients on the dexamethasone arm performed more poorly on a measure of fluid reasoning ($P = 0.02$). They also tended to be more likely to be enrolled in special education (dexamethasone, 33% vs. prednisone, 20%, $P = 0.09$).

Conclusions—Dexamethasone has well documented benefit in treatment of ALL. Although formal testing provided little indication of increased risk for neurotoxicity relative to prednisone, the somewhat greater utilization of special education services by patients treated with dexamethasone merits further investigation.

Keywords

acute lymphoblastic leukemia; behavior; children; cognition; dexamethasone

INTRODUCTION

Glucocorticoids are an important and universal component of treatment for acute lymphoblastic leukemia (ALL). Although steroid therapy for many years was given in the form of prednisone, investigators have increasingly shifted to dexamethasone since it has better CNS penetration and a longer half-life [1]. Indeed, several randomized trials have demonstrated that dexamethasone has greater therapeutic efficacy [1–3].

A persistent concern in designing therapy protocols for childhood ALL and other cancers, however, is the potential impact of the disease and its treatment on the brain and, hence, on the child's development and longer term functional outcomes. Concerns about these late neurocognitive and neurobehavioral effects have focused primarily on the impact of treatment with cranial radiation, intrathecal chemotherapy, and high-dose intravenous methotrexate, but questions have also been raised about whether corticosteroids contribute to neurocognitive late effects. These agents can have acute impacts on cognition, behavior, and mood in children who are on treatment for ALL [4,5]. Use of corticosteroids in children and adolescents also raises the concern that drug exposure could adversely affect the developing brain, with risk of longer-term and potentially more permanent functional effects.

There is limited and conflicting evidence regarding differences between dexamethasone and prednisone in terms of neurocognitive functioning. We previously reported that children who had been treated on a protocol that included prednisone as the steroid component of therapy showed better performance on some cognitive tasks than did those treated on a subsequent protocol where dexamethasone was used [6]. Another study suggested that children treated

on a protocol using dexamethasone exhibited more behavior problems during therapy than children treated with prednisone [7]. These studies were not controlled, however.

Kadan-Lottick et al. [8] studied late cognitive effects in 92 patients enrolled on a Children's Cancer Group (CCG) protocol who had been randomized to therapy with dexamethasone or prednisone. They found no difference in outcomes between patients treated on the two arms of the protocol on measures of intelligence, visuomotor integration, attention, or memory. The only exception was a difference in single word reading, which favored the patients on the prednisone arm. The rate of special education utilization was higher in the dexamethasone arm, but the difference did not achieve statistical significance. In another study [9], no differences were found in Health Related Quality of Life for children who had been randomized to prednisone or dexamethasone. In yet another study, young children being treated for ALL showed an increase in behavioral problems while on steroid therapy, but these problems were not related to steroid type [5].

In the present study, we evaluated neuropsychological outcomes for 170 patients treated on Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocol 00-01 who had been randomized to treatment with prednisone or dexamethasone as the steroid component of therapy. On this protocol, dexamethasone was associated with superior 5-year event-free survival ($90 \pm 2\%$ dexamethasone vs. $81 \pm 3\%$ prednisone, $P = 0.01$) [10]. Patients randomized to dexamethasone had a higher incidence of infection, and older patients (10–18 years) on the dexamethasone arm experienced a higher rate of both osteonecrosis and fracture [10].

We hypothesized that patients randomized to the dexamethasone arm would exhibit greater cognitive and behavioral deficits relative to those treated with prednisone. Because of the known impact of glucocorticoid steroids on hippocampus and memory [11,12], we further hypothesized that these differences would be particularly evident on memory tasks.

PATIENTS AND METHODS

Patients

Children and adolescents between the ages of 1 and 18 years with newly diagnosed ALL (excluding mature B-cell ALL) were eligible for enrollment on Protocol 00-01 from the following DFCI ALL Consortium institutions: DFCI/Boston Children's Hospital (Boston, MA); Columbia University Medical Center, Morgan Stanley Children's Hospital of New York-Presbyterian (New York, NY); Hospital Sainte Justine (Montreal, QC, Canada); Le Centre Hospitalier de L'Universite Laval (Quebec City, QC, Canada); Maine Children's Cancer Program (Scarborough, Maine); McMaster Children's Hospital (Hamilton, ON, Canada); San Jorge Children's Hospital (San Juan, PR); Tulane Hospital for Children (New Orleans, LA); and University of Rochester Medical Center (Rochester, NY). The institutional review board of each participating institution approved the protocol before enrolling patients. Informed consent was obtained from parents or guardians for each patient prior to study enrollment and the initiation of therapy.

Risk Groups

Patients were classified and treated as standard-risk (SR) or high-risk (HR) [13]. SR patients met all of the following criteria: age 1–9.99 years, white blood cell (WBC) count less than $50 \times 10^9/L$, B-precursor phenotype, diagnostic CSF with fewer than five leukocytes per high-power field (CNS-1 or CNS-2 status), and absence of a mediastinal mass. All other patients were designated as high-risk. Patients with the Philadelphia chromosome were treated as HR but underwent allogeneic hematopoietic stem cell transplantation after achieving complete remission. These patients were excluded from the study. Patients found to have an MLL-gene rearrangement received an additional intensification cycle after achieving complete remission and then continued on the HR arm of the protocol. These patients were included in the study.

Therapy

Details of treatment are summarized in Table I. All patients received prednisone during the induction phase. Patients with persistent leukemia at the end of the first month of treatment were removed from the protocol and given alternative therapy. All patients received one dose of high-dose methotrexate (4 g/m^2) during the remission induction phase. HR patients received cranial radiation therapy beginning at week 7 of therapy at a dose of 12 Gy for those who were CNS-1 at diagnosis and 18 Gy for those who were CNS-2 or CNS-3. SR patients did not receive cranial radiation, but did receive three additional doses of intrathecal chemotherapy during the first year of treatment as compared to high-risk patients. Therapy for all patients was discontinued after 24 months of continuous complete remission.

Corticosteroid Randomization

Participation in the corticosteroid randomization was not mandatory. For patients consenting to participation, randomization assignments were prepared by the study statistician using a permuted blocks algorithm with balancing to assure that a treatment imbalance within an institution was no greater than three patients. Randomization was stratified by risk group. Although patients/guardians and treating-providers were not blinded to the form of steroid assigned, the psychologists who performed the testing were blinded.

SR patients were randomly assigned to receive either dexamethasone at a dose of $6 \text{ mg/m}^2/\text{day}$ or prednisone at a dose of $40 \text{ mg/m}^2/\text{day}$, administered as 5-day pulses every 3 weeks beginning at week 7, until the completion of therapy. HR patients received either dexamethasone at a dose of $18 \text{ mg/m}^2/\text{day}$ or prednisone at a dose of $120 \text{ mg/m}^2/\text{day}$ during the 30-week intensification phase, and then received the same dose of steroid as SR patients during the continuation phase. Steroid dosing differed from prior DFCI protocols in that HR patients had previously received doses three times higher than those received by SR patients during both the intensification and continuation phases. Patients who declined to participate in the randomization and those with the Philadelphia chromosome were directly assigned to receive prednisone. Corticosteroids were permanently discontinued in the setting of symptomatic, radiographically confirmed osteonecrosis and were temporarily held for bone fracture (and resumed when the fracture was healed).

Neuropsychological Follow-Up Study

The neuropsychological follow-up study was performed as a separate clinical trial after approval by local institutional review boards and in accordance with an assurance filed with and approved by the Department of Health and Human Services. Informed consent was obtained from each participant or each participant's guardian, and assent was obtained from minors.

The neuropsychological follow-up study was opened in eight of the nine centers who had participated in Protocol 00-01. Patients were eligible to enroll on this trial if they had been enrolled on Protocol 00-01 and remained in first complete remission (no prior relapse). Patients were excluded if parents reported pre-existing neurodevelopmental problems that could impair cognitive function, such as premature birth, developmental or learning delays, birth trauma, meningitis, or a neurogenetic syndrome. Since these conditions were varied and difficult to anticipate on an a priori basis, a decision to exclude was based on the following principles: (1) condition known on the basis of extant clinical research to be associated with adverse neurodevelopmental sequelae; and (2) condition occurred or was present prior to the leukemia diagnosis. Psychologists at each participating center performed testing on patients who had been treated at that center.

Neuropsychological testing was performed at a median of 5.8 years after diagnosis of leukemia in both groups (prednisone, range 4.8–8.6; dexamethasone, range 5.8–8.6). We used a relatively brief neuropsychological battery to enhance reliability and comparability of data across institutions and to encourage compliance. This approach also facilitated testing for a study group in which a substantial portion of the children did not speak English.

Neuropsychological Test Battery

Table II lists the neuropsychological battery. Adaptations were made to accommodate the three languages of our participants, who lived in the United States, Puerto Rico (Spanish), or Quebec (French). To the extent possible, we chose verbal measures with published versions in English and Spanish, but these needed to be translated to Canadian French.

IQ was estimated based on two subtests from the Wechsler Abbreviated Scale of Intelligence (WASI): Vocabulary and Matrix Reasoning. The correlation between the WASI 2-subtest IQ estimate and the WISC-III Full Scale IQ is 0.81 [14]. For non-English speakers, the same tests from the most recent edition of the Wechsler Intelligence Scale for Children (WISC) or Wechsler Adult Intelligence Scale (WAIS) were substituted. We also measured working memory and processing speed (which are often depressed in children with learning problems), the ability to copy and recall a complex design, and memory for complex narrative material. Screening measures of academic skills and structured parent questionnaires to assess behavior and affect in everyday life were also administered. The Behavioral Assessment System for Children-2 (BASC-2) yields scales characterizing mood and behavior symptoms as well as positive adaptation. The Behavior Rating Inventory of Executive Function yields scales indicative of problems with behavioral regulation and metacognitive skills. We additionally asked parents whether the child was currently receiving special education services.

Statistical Methods

Fisher's exact and *t*-tests (two-sided) were used to compare children on the two arms of the protocol in terms of various characteristics that might affect their cognitive performance. The Wilcoxon rank sum test was used to evaluate differences in neuropsychological test scores. This non-parametric test limited the impact of extreme values in the distribution. Because of the a priori direction of the expected group difference, one-sided Wilcoxon tests were used. Hodges–Lehmann Estimates evaluated the median of all possible differences between the groups and generated 95% CIs. A chi-squared test was used to compare the frequency of special education utilization on the two arms of the protocol.

With the present sample size, the study had 89% power to declare a specific two-sided *t*-test statistically significant for a constant effect size of 0.5 SD, assuming normality and independence among all tests. This is a medium effect size that would be clinically meaningful, and is in line with estimates from non-randomized studies.

RESULTS

The CONSORT table is displayed as Figure 1. Children were recruited for the neuropsychological testing at a target of 5 years post-diagnosis. The final sample included 170 children, 76 randomized to prednisone and 94 to dexamethasone. Participants on the two steroid arms did not differ with respect to age at diagnosis or testing, risk group, sex distribution, parent education, or primary language, nor did they differ on any of the medical variables, including CRT dose, fracture, and osteonecrosis (Table III).

Comparison of eligible patients who were tested with those who were not tested revealed that those who were not tested had been older at diagnosis ($P<0.001$), more likely to be classified as HR ($P<0.05$), and more likely to be treated on the prednisone arm ($P<0.05$). There was no difference in the sex distribution ($P>0.30$). The pattern of these differences suggests that patients who were older, and thus would also be more likely to be treated as HR patients, were less likely to consent to participation. Fewer patients on the dexamethasone arm were excluded because of relapse, and we can also conjecture that their parents were more inclined to consent to participate because of concerns about neuropsychological sequelae.

Neuropsychological Tests and Questionnaires

Tables IV and V display the outcomes by group. For the cognitive tests, the only statistically significant difference was for the WASI Matrix Reasoning. Since it is one of the two subtests used to calculate an estimated IQ, there was also a marginally significant difference for IQ. There were no group differences for the Woodcock-Johnson Achievement tests, the TOMAL Story Memory, or the (raw) organization scores for the Rey-Osterrieth Complex Figure (Table IV).

For the Rey Figure, we also calculated the proportion of each group with scores below the 10th percentile to determine whether there was a group difference in the frequency of low scores and/or an elevation relative to age norms. Although the proportion was slightly higher among the dexamethasone group for the copy (36% vs. 30%), immediate (37% vs. 33%),

and delayed recall (31% vs. 25%), none of these differences reached statistical significance. For both groups, however, the proportion of individuals with low scores was approximately three times the normative expectation.

Table V shows statistics for the parent questionnaire measures. There were no differences on any scale. Interactions with sex, risk group, and age at diagnosis were not statistically significant for either the test or questionnaire measures.

Special Education Utilization

Even though there were minimal group differences based on tests and questionnaires, the findings were suggestive of differences in special education utilization. Patients who were 18 or older at the time of evaluation and thus unlikely to have access to special education services (prednisone, $N = 10$; dexamethasone, $N = 9$) were excluded from this analysis, and data were missing for three other patients (prednisone, $N = 1$; dexamethasone, $N = 2$). With 148 patients providing data, 13/65 (20%) from the prednisone group were receiving special education services compared with 27/83 (32.5%) from the dexamethasone group ($P = 0.09$). Interactions between steroid group and age at diagnosis (<60 months vs. >60 months), risk group, and sex were not statistically significant.

DISCUSSION

The findings from this randomized trial found little indication that dexamethasone, when compared to prednisone, is associated with greater risk for neurocognitive late effects, including on measures of memory. Our results generally confirm those previously reported from a similar trial carried out by the Children's Cancer Group (CCG) [8]. Based on standard testing and questionnaires, we noted only minimal differences between the groups. Our study revealed a modest decrement on an IQ measure, and the CCG study found a difference for a reading measure.

In both studies, however, special education utilization was higher among patients treated on the dexamethasone arm. In the CCG study, the percentages were 16% versus 5%, but the group difference did not achieve statistical significance, most likely because of insufficient statistical power. In our study, the overall percentages were much higher (36% vs. 20%) and the group difference approached statistical significance. These differences in special education utilization, a "real-world assay," may be clinically meaningful, suggesting vulnerability in the dexamethasone group that was not detected by the tests or questionnaires. Although the group difference in special education utilization was not of sufficient magnitude to achieve statistical significance, the consistent pattern across studies suggests that future studies should explore this indicator in greater detail.

Even though there were few differences between steroid groups, the cohort as a whole showed compromise in some neurocognitive competencies that likely have functional implications. We have consistently found that ALL survivors show deficits on the Rey-Osterrieth Complex Figure Test, even when estimated IQ and academic skills are in the average range [15,16]. In the present study, the proportion of children with scores at or below the 10th percentile, that is, in the deficit range, was elevated threefold above

normative expectation. Poor performance on this task is associated with learning disabilities [17], suggesting increased risk for learning problems in this population in general.

It is important to stress, however, that mean scores on nearly all outcomes approximated the mean for the general population. This suggests that any adverse neurocognitive and neurobehavioral sequelae of therapy on DFCI Protocol 00-01, irrespective of steroid therapy, are relatively mild, even though approximately 40% of patients were treated with cranial radiation therapy. We have previously noted the variation between the generally positive neuropsychological outcomes on DFCI protocols and some other protocols that have documented more prominent deficits [18], particularly for patients treated with cranial radiation therapy [19]. The reasons for this variation, however, remain uncertain. Moreover, in the absence of a healthy control group, it is not possible to address whether these average scores would still represent a decrement relative to demographically comparable peers.

In sum, based on both tests and questionnaires, we found little evidence for additional neurotoxicity associated with dexamethasone compared with prednisone in the treatment of ALL. Patients on the dexamethasone arm did utilize special education at somewhat higher rates, however. Although we did not detect clinically significant neurocognitive risks associated with dexamethasone, we and others have demonstrated that dexamethasone is associated with a higher risk of musculoskeletal toxicity, including myopathy, osteopenia, fractures, and osteonecrosis [3,10]. Importantly, dexamethasone is more effective than prednisone in preventing relapse in children with ALL [1–3,10]. Thus, future clinical trials should focus on how to optimize its use, either reserving it for those at highest risk of relapse, or investigating alternative dosing regimens which may be similarly efficacious but with less risk for toxicity [20].

Acknowledgments

This study was supported by Grant 2 P01 CA 68484 from the National Cancer Institute, the Michael J. Garil Fund for Leukemia Research, and in part by Intellectual and Developmental Disabilities Research Center grant P30-HD18655. This work is all original and has not been presented elsewhere. This is an original work.

References

1. Inaba H, Pui C-H. Glucocorticoid use in acute lymphoblastic leukaemia. *Lancet Oncol.* 2010; 11:1096–1106. [PubMed: 20947430]
2. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: A report from the Children's Cancer Group. *Blood.* 2003; 101:3809–3817. [PubMed: 12531809]
3. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol.* 2005; 129:734–745. [PubMed: 15952999]
4. Drigan R, Spirito A, Gelber RD. Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. *Med Pediatr Oncol.* 1992; 20:13–21. [PubMed: 1727206]
5. Mrakotsky CM, Silverman LB, Dahlberg SE, et al. Neurobehavioral side effects of corticosteroids during active treatment for acute lymphoblastic leukemia in children are age-dependent: Report from Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *Pediatr Blood Cancer.* 2011; 57:492–498. [PubMed: 21560226]

6. Waber DP, Carpentieri SC, Klar N, et al. Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone [comment]. *J Pediatr Hematol Oncol*. 2000; 22:206–213. [PubMed: 10864051]
7. Marcoux S, Robaey P, Krajinovic M, et al. Predictive factors of internalized and externalized behavioral problems in children treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2012; 58:971–977. [PubMed: 22287274]
8. Kadan-Lottick NS, Brouwers P, Breiger D, et al. A comparison of neurocognitive functioning in children previously randomized to dexamethasone or prednisone in the treatment of childhood acute lymphoblastic leukemia. *Blood*. 2009; 114:1746–1752. [PubMed: 19546477]
9. Eiser C, Davies H, Jenney M, et al. HRQOL implications of treatment with dexamethasone for children with acute lymphoblastic leukemia (ALL). *Pediatric Blood Cancer*. 2006; 46:35–39. [PubMed: 15926164]
10. Vrooman LM, Stevenson K, Supko JG, et al. Post-induction dexamethasone and individualised dosing of *E. coli* L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: Results from the Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *J Clin Oncol*. 2013; 31:1202–10. [PubMed: 23358966]
11. Packan DR, Sapolsky RM. Glucocorticoid endangerment of the hippocampus: Tissue, steroid and receptor specificity. *Neuroendocrinology*. 1990; 51:613–618. [PubMed: 2113998]
12. Newcomer JW, Selke G, Melson AK, et al. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry*. 1999; 56:527–533. [PubMed: 10359467]
13. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for Children with Acute Lymphoblastic Leukemia. *Blood*. 2007; 109:896–904. [PubMed: 17003366]
14. Wechsler, D. Wechsler Abbreviated Scale of Intelligence. New York: Psychological Corporation; 1999.
15. Waber DP, Silverman LB, Catania L, et al. Outcomes of a randomized trial of hyperfractionated cranial radiation therapy (18 Gy) for treatment of high-risk acute lymphoblastic leukemia: Therapeutic efficacy and neurotoxicity. *J Clin Oncol*. 2004; 22:2701–2707. [PubMed: 15226337]
16. Waber DP, Turek J, Catania L, et al. Neuropsychological outcomes from a randomized trial of triple intrathecal chemotherapy compared with 18 Gy cranial radiation as CNS treatment in acute lymphoblastic leukemia: Findings from Dana-Farber Cancer Institute ALL Consortium Protocol 95-01. *J Clin Oncol*. 2007; 25:4914–4921. [PubMed: 17971588]
17. Waber DP, Bernstein JH. Performance of learning-disabled and non-learning-disabled children on the Rey-Osterrieth Complex Figure (ROCF): Validation of the developmental scoring system. *Dev Neuropsychol*. 1995; 11:237–252.
18. Waber DP, Shapiro BL, Carpentieri SC, et al. Excellent therapeutic efficacy and minimal late neurotoxicity in children treated with 18 grays of cranial radiation therapy for high-risk acute lymphoblastic leukemia: A 7-year follow-up study of the Dana-Farber Cancer Institute Consortium Protocol 87-01. *Cancer*. 2001; 92:15–22. [PubMed: 11443604]
19. Spiegler BJ, Kennedy K, Maze R, et al. Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate. *J Clin Oncol*. 2006; 24:3858–3864. [PubMed: 16921038]
20. Mattano LA Jr, Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: Results from the CCG-1961 randomised cohort trial. *Lancet Oncol*. 2012; 13:906–915. [PubMed: 22901620]
21. Wechsler, D. Wechsler Intelligence Scale for Children. 4. New York, NY: Psychological Corporation; 2003.
22. Wechsler, D. Wechsler Adult Intelligence Scale. 3. San Antonio, TX: The Psychological Corporation; 1997.
23. Bernstein, JH., Waber, D. Developmental Scoring System for the Rey-Osterrieth Complex Figure. Odessa, FL: Psychological Assessment Resources; 1996.

24. Reynolds, CR., Bigler, ED. Test of memory and learning. Austin, TX: Pro-Ed; 1994.
25. Woodcock, RW., McGrew, KS., Mather, N. Woodcock-Johnson III. Itasca, IL: Riverside Publishing; 2001.
26. Reynolds, CR., Kamphaus, RW. Behavior Assessment System for Children. 2. Circle Pines, MN: American Guidance Service; 2004.
27. Gioia, GA., Isquith, PK., Guy, SC., et al. Behavior rating inventory of executive function. Odessa, FL: Psychological Assessment Resources; 2000.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.
CONSORT Table.

TABLE I

Therapy for Patients on DFCI ALL Consortium Protocol 00-01

Induction (4 weeks)	<p>VCR 1.5 mg/m² weekly (maximum 2 mg), days 0, 7, 14, 21</p> <p>Prednisone 40 mg/m²/day, days 0–28</p> <p>DOX 30 mg/m²/dose, days 0 and 1 (HR patients: with dexrazoxane 300 mg/m²/dose)</p> <p>MTX 4 g/m² (8–24 hours after doxorubicin) with leucovorin rescue</p> <p>EC-Asnase 25,000 IU/m² IM × 1 dose</p> <p>IT cytarabine, day 0^{a,b}; IT MTX/cytarabine/hydrocortisone × 1 dose, day 14</p>
CNS therapy (3 weeks)	<p>VCR 2 mg/m² (maximum 2 mg) day 1; 6-MP 50 mg/m²/day orally at bedtime × 14 days</p> <p>SR patients: IT MTX/cytarabine/hydrocortisone twice weekly × 4 doses</p> <p>HR patients: also DOX 30 mg/m² day 1, with dexrazoxane 300 mg/m²; cranial radiation^c</p>
Intensification (30 weeks)	<p>Every 3 week cycles</p> <p>VCR 2 mg/m² (maximum 2 mg), day 1; 6-MP 50 mg/m²/day orally at bedtime × 14 days; MTX 30 mg/m² (1 mg/kg if <0.6 m²) IV or IM weekly</p> <p>Corticosteroid, randomized</p> <p>Dexamethasone 6 mg/m²/day ÷ bid, orally, days 1–5, <i>or</i></p> <p>Prednisone 40 mg/m²/day ÷ bid, orally, days 1–5</p> <p>EC-Asnase randomized</p> <p>Fixed-dosing: 25,000 IU/m² IM, weekly × 30, <i>or</i></p> <p>Individualized dosing: 12,500 IU/m² IM (starting dose) weekly × 30; dose adjusted every 3 weeks to maintain nadir serum asparaginase activity between 0.1 and 0.14 IU/ml</p> <p>IT MTX/cytarabine/hydrocortisone at start of a cycle q 9 weeks × 6 doses, then q 18 weeks through completion of therapy (at start of a cycle)</p> <p>HR patients: same as above, except higher steroid dose (prednisone 120 mg/m²/day, days 1–5, <i>or</i> dexamethasone 18 mg/m²/day, days 1–5), DOX 30 mg/m² day 1 of each cycle (cumulative dose 300 mg/m²) with dexrazoxane 300 mg/m²/dose, no weekly MTX IV/IM until doxorubicin completed, and IT therapy of MTX/cytarabine q 18 weeks</p>
Continuation (74 weeks)	<p>Every 3 week cycles</p> <p>SR: same as intensification except no asparaginase</p> <p>HR: same as SR patients (including lower steroid dose)</p>

IT, intrathecal; HR, high-risk; SR, standard-risk; VCR, vincristine; DOX, doxorubicin; MTX, methotrexate; EC-Asnase, *E. coli* asparaginase; 6-MP, 6-mercaptopurine; IM, intramuscular; NSAA, nadir serum asparaginase activity.

^aDosed according to age;

^bPatients with CNS leukemia at diagnosis (CNS-2 and CNS-3) received twice weekly doses of IT cytarabine until CSF was clear of blast cells on three consecutive examinations;

^cOnly HR patients received cranial radiation, 1200 cGy cranial radiation delivered as 150 cGy daily fractions for 8 days, except for patients classified as CNS-2 or CNS-3 at diagnosis or during induction therapy who received 1,800 cGy delivered as 180 cGy daily fractions for 10 days.

TABLE II

Neuropsychological Test Battery

Test	Function	Type of measure
Wechsler Intelligence Scales (WASI, WISC-IV or WAIS-III) [14,21,22]		Test
Vocabulary	Vocabulary knowledge/reasoning	
Matrix Reasoning	Non-verbal reasoning	
Digit Span	Working memory	
Coding	Processing speed	
Rey-Osterrieth Complex Figure (ROCF) [23]		Test
Copy	Perceptual organization/executive function	
Immediate and delayed recall	Memory for complex visual material	
Test of Memory and Learning (TOMAL)—Memory for Stories [24]		Test
Immediate and Delayed Recall	Memory for complex verbal material	
Woodcock-Johnson Psychoeducational Battery—III (WJ-III) [25]		Test
Passage comprehension	Reading comprehension	
Calculation	Arithmetic calculation	
Behavioral Assessment System for Children—Second Edition (BASC-2)—parent [26]	Psychosocial adjustment	Questionnaire
Behavioral Rating Inventory of Executive Function (BRIEF)—parent [27]	Executive function in daily life	Questionnaire

TABLE III

Demographic and Medical Characteristics of Patients Who Received Neuropsychological Testing According to Randomization

Patient characteristics	Prednisone (N = 76)	Dexamethasone (N = 94)	P-value
Age (years) at diagnosis			
Mean (SD)	5.7 (4.2)	5.4 (3.7)	n.s.
Median (range)	4.0 (1.0–17.8)	3.9 (1.0–17.6)	
Age <60 months at diagnosis			
N (%)	45 (59.2)	58 (61.7)	n.s.
Age (years) at evaluation			
Mean (SD)	11.6 (4.3)	11.4 (3.8)	n.s.
Median (range)	10.2 (6.5–23.1)	10.3 (6.3–23.2)	
Standard risk, N (%)	45 (59.2)	64 (68.1)	n.s.
Male, N (%)	42 (55.3)	44 (46.8)	n.s.
Native language, N (%)			
English	35 (46.1)	38 (41.3)	
Spanish	12 (15.8)	15 (16.3)	n.s.
French	24 (31.6)	29 (31.5)	
Other/bilingual	5 (6.6)	10 (10.9)	
Mother's education, N (%)			
Less than high school	4 (5.5)	5 (5.5)	n.s.
High school graduate	7 (9.6)	14 (15.4)	
Some college/associate	21 (28.8)	27 (29.7)	
College graduate	25 (34.3)	29 (31.9)	
Postgraduate education	16 (21.9)	16 (17.6)	
CRT dose, N (%)			
0 Gy	44 (58.6)	64 (68.0)	n.s.
12 Gy	23 (30.6)	21 (22.3)	
18 Gy	8 (10.6)	9 (9.6)	
MLL rearrangement, N (%)	2 (2.0)	0 (0.0)	n.s.
Fracture, N (%)	9 (11.8)	13 (13.8)	n.s.
Osteonecrosis, N (%)	2 (2.6)	4 (4.3)	n.s.

TABLE IV

Medians, Minimums, Maximums, 25th and 75th %iles, Wilcoxon Tests, and Hodges–Lehmann Estimates (Confidence Intervals) for Neuropsychological Tests

	Prednisone (N = 76)					Dexamethasone (N = 94)					Wilcoxon <i>P</i> -value	Hodges-Lehmann Estimate Median (Diff. = PRED – DEX) and 95% CI	
	N	Min	P25	Median	P75	Max	N	Min	P25	Median			P75
Wechsler Intelligence Scale (Scaled Scores)													
Vocabulary	76	3.0	9.0	11.0	14.0	18.0	94	3.0	9.0	11.0	13.0	19.0	0 (–1,1)
Matrix Reasoning	76	5.0	9.5	12.0	13.0	15.0	94	3.0	8.0	10.0	13.0	16.0	1 (0,2)
Digit Span	76	3.0	7.5	9.0	12.0	17.0	94	3.0	7.0	9.0	11.0	19.0	0 (–1,1)
Coding/Digit Symbol	75	4.0	8.0	10.0	12.0	19.0	94	3.0	8.0	10.0	11.0	19.0	0 (–1,1)
Estimated Full Scale IQ (Standard Score)	76	78.0	96.0	109.0	118.0	141.0	94	67.0	93.0	102.0	115.0	144.0	0.06
Woodcock Johnson Psychoeducational Battery—III (Standard Scores)													
Passage Comprehension ^a	48	77.0	89.5	99.0	107.0	128.0	60	69.0	89.0	97.5	105.0	132.0	2 (–3,7)
Calculation ^b	50	63.0	93.0	102.5	109.0	147.0	65	66.0	91.0	99.0	107.0	140.0	3 (–2,8)
Test of Memory and Learning (TOMAL) Story Recall (Scaled Scores)													
Immediate	64	6.0	9.0	11.0	13.0	19.0	90	4.0	10.0	11.0	13.0	16.0	0 (–1,1)
Delay	60	5.0	9.0	11.0	12.5	19.0	87	5.0	10.0	11.0	13.0	18.0	0 (–1,1)
Rey-Osterrieth Complex Figure (Raw Score)													
Copy Organization	74	2.0	4.0	6.0	9.0	13.0	94	1.0	3.0	6.0	8.0	13.0	0.5 (0,1)
Immediate Recall	73	1.0	2.0	5.0	9.0	13.0	94	1.0	2.0	4.5	8.0	13.0	0 (–1,1)
Delayed Recall	70	1.0	2.0	5.0	9.0	13.0	90	1.0	2.0	5.0	9.0	13.0	0.5 (0,1)

^aEnglish and Spanish combined;

^bEnglish, Spanish, and French combined; bolded rows statistically significant;

Scaled Scores, mean $\pm$ SD = 10 $\pm$ 3; Standard Scores, mean $\pm$ SD = 100 $\pm$ 15; IQ, mean $\pm$ SD = 100 $\pm$ 15. The 25th and 75 %iles should be 2/3 SD.

TABLE V

Medians, Minimums, Maximums, 25th and 75th %iles, Wilcoxon Tests, and Hodges–Lehmann Estimates (Confidence Intervals) for BASC and BRIEF Scales

	Prednisone (N = 76)						Dexamethasone (N = 94)						Wilcoxon <i>P</i> -value	Hodges–Lehmann Estimate Median (Diff. = PRED – DEX) and 95% CI
	N	Min	P25	Median	P75	Max	N	Min	P25	Median	P75	Max		
Behavioral Assessment System for Children-2 (T-score)														
Externalizing	69	34.0	42.0	47.0	55.0	77.0	88	36.0	42.0	47.0	54.5	100.0	0.44	0 (–3.3)
Internalizing	69	30.0	41.0	48.0	57.0	74.0	88	35.0	43.0	50.5	60.5	92.0	0.19	–2 (–5.2)
Behavioral Symptoms Index	69	34.0	42.0	49.0	56.0	77.0	88	35.0	42.0	48.0	56.5	93.0	0.43	0 (–3.3)
Adaptive skills ^a	69	29.0	45.0	52.0	58.0	73.0	88	23.0	43.0	51.0	59.0	71.0	0.39	1 (–3.4)
Behavioral Rating Inventory of Executive Function (T-score)														
Behavioral Regulation Index	65	35.0	41.0	49.0	55.0	97.0	86	36.0	41.0	47.0	57.0	78.0	0.41	0.5 (–4.3)
Metacognitive Index	65	35.0	44.0	51.0	62.0	82.0	87	34.0	45.0	51.0	60.0	81.0	0.45	0 (–4.4)
General Executive Composite	64	35.0	43.5	50.0	59.0	83.0	86	34.0	44.0	50.0	61.0	84.0	0.34	–0.5 (–4.3)

^aHigher score indicates better functioning; for all other scales, high scale indicates more problems.

T-score, mean $\pm$ SD = 50 $\pm$ 10. The 25th and 75th %iles should be 2/3 SD.