Published in final edited form as:

Pediatr Blood Cancer. 2016 February ; 63(2): 255–261. doi:10.1002/pbc.25793.

Outcome of children with standard-risk T-lineage acute lymphoblastic leukemia – comparison among different treatment strategies

Yousif Matloub¹, Linda Stork², Barbara Asselin³, Stephen P. Hunger⁴, Michael Borowitz⁵, Tamekia Jones⁶, Bruce Bostrom⁷, Julie M. Gastier-Foster^{8,9,10}, Nyla A. Heerema⁹, Andrew Carroll¹¹, Naomi Winick¹², William L. Carroll¹³, Bruce Camitta¹⁴, Meenakshi Devidas¹⁵, and Paul S. Gaynon¹⁶

¹Rainbow Babies & Children's Hospital, Division of Hematology-Oncology, Case Western Reserve University, Cleveland, Ohio ²Doernbecher Children's Hospital, Division of Hematology-Oncology, Oregon Health & Science University, Portland, Oregon ³Golisano Children's Hospital, Department of Pediatrics, University of Rochester Medical Center, Rochester, New York ⁴Children's Hospital of Philadelphia, Philadelphia, Pennsylvania ⁵Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland ⁶Children's Foundation Research Institute, University of Tennessee Health Science Center, Memphis, Tennessee ⁷Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota ⁸Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio ⁹Department of Pathology, The Ohio State University College of Medicine, Columbus, Ohio ¹⁰Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio ¹¹Department of Genetics, University of Alabama at Birmingham, Alabama ¹²Division of Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas, Texas ¹³New York University Cancer Institute, New York, New York ¹⁴Midwest Center for Cancer and Blood Disorders, Pediatric Hematology-Oncology, Milwaukee, Wisconsin ¹⁵Department of Biostatistics, Colleges of Medicine, Public Health & Health Professions, Children's University of Florida, Gainesville, Florida ¹⁶Division of Hematology-Oncology, Children's Hospital Los Angeles, University of Southern California, Los Angeles, California

Abstract

Background—Children with T-lineage acute lymphoblastic leukemia ALL (T-ALL) historically have had inferior outcomes to children with precursor-B ALL (B-ALL). After 1995, the

---

Corresponding Author: Yousif Matloub, MD, Rainbow Babies & Children's Hospital, Pediatric Hematology/Oncology, Cleveland, OH 44106, Phone: 216-844-3345, FAX: 216-844-5431, yousif.matloub@uhhospitals.org.

Authorship

YM chaired one of the studies and wrote the manuscript. LS and BA chaired the other two studies and contributed in writing the manuscript. SPH contributed in writing and reviewing the manuscript. MB analyzed the immunophenotypic results and reviewed the manuscript. TJ and MD performed the statistical analyses and contributed in writing and reviewing the manuscript. BB co-chaired one of the studies and reviewed and edited the manuscript. NH performed the cytogenetic analyses and contributed in reviewing and editing the manuscript. JMG-F, NW, WC, BC and PSG contributed in reviewing and editing the manuscript.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Children's Cancer Group (CCG) treated patients with B- and T-ALL according to National Cancer Institute (NCI) risk criteria, basing risk stratification on age and white blood cell count (WBC) regardless of immunophenotype. The Pediatric Oncology Group (POG) treated all patients with T-ALL on separate, generally more intensive protocols than those used to treat patients with B-ALL.

Procedure—We compared outcomes of children with T-ALL and NCI standard-risk (SR) criteria treated on CCG and POG trials between 1996 and 2005. CCG SR-ALL 1952 and 1991 enrolled 80 and 86 patients with T-ALL, respectively, utilizing a reduced intensity Berlin-Frankfurt-Munster (BFM) backbone. Treatment was intensified for slow early responders (SERs) and only patients with overt central nervous system (CNS) leukemia received cranial irradiation. Eighty-four patients with T-ALL and SR features were enrolled on POG 9404 comprising more intensive therapy with all patients receiving cranial irradiation.

Results—The 7-year event-free survival (EFS) for patients with SR T-ALL on CCG-1952, CCG-1991, and POG-9404 were $74.1 \pm 5.8\%$, $81.8 \pm 5.3\%$, and $84.2 \pm 4.3\%$, respectively ($p = 0.18$). Overall 7-year survivals were $86.1 \pm 4.6\%$, $88.3 \pm 4.4\%$, $89.1 \pm 3.6\%$, respectively ($p = 0.84$).

Conclusions—Comparable high rates of EFS and long-term survival were achieved with all three regimens, with the CCG regimens utilizing a less intensive chemotherapy backbone without prophylactic cranial irradiation for patients with SR T-ALL.

Keywords

T-cell leukemia; childhood acute leukemia; childhood leukemia

Introduction

T-ALL constitutes approximately 15% of pediatric acute lymphoblastic leukemia (ALL).[1–4] Historically, patients with T-ALL has had an inferior outcome compared to those with B-ALL.[5–7] Patients with T-ALL tend to experience more induction failures and extramedullary relapses than their B-ALL counterparts.[8],¹³ They also frequently present with unfavorable clinical features, such as male gender, older age, high white blood cell count (WBC), bulky extramedullary disease, and CNS involvement.[1,2,9–11] Prognosis of children with T-ALL has seen significant improvement as their treatment intensified.[4,8,12,13]

In 1996, an NCI workshop published recommendations which defined specific prognostic factors that identified patients with B-ALL as either SR or high-risk (HR) based on risk of relapse.[14] At that time, the treatment strategies employed by the major study groups for treatment of T-cell immunophenotype ALL varied widely. Thus, no outcome data based on uniform classification criteria were available for patients with T-ALL. When the NCI risk criteria are applied to children with T-ALL, 70% meet the age and WBC criteria for high-risk ALL, compared to only about one-third of children with B-ALL.[14],[4]

Starting in 1996, the legacy CCG treated patients with T-ALL according to the NCI risk defined criteria with therapy based on modified BFM protocols regardless of immunophenotype.[14] Patients with either B- or T-ALL were enrolled on protocols

designed for treatment of either SR or HR-ALL based on the NCI criteria of age and WBC at diagnosis. In contrast, POG treated all patients with T-ALL on separate, generally more intensive protocols than they used for those with B-ALL. In light of the favorable outcomes for patients with T-ALL reported by the DFCI protocol 87-01[15], POG-9404 was developed exclusively for patients with T-ALL and advanced stage lymphoblastic lymphoma with the same therapy regardless of age and initial WBC.[15,16] This report compares the outcomes of patients with T-ALL and NCI-SR features of age 1–9.99 years and initial WBC $< 50 \times 10^9/\mu\text{L}$ treated on the CCG 1952 and 1991 SR-ALL trials with those of the contemporaneous POG 9404 T-ALL study.

Patients and Methods

The NCI and institutional review boards of all participating CCG or POG institutions approved the studies. Written, informed consent was obtained prior to patient registration from parents or guardians according to the local institutional guidelines, the Department of Health and Human Services regulations and the Declaration of Helsinki.

Treatment protocols

CCG-1952 was open for accrual from May 1996 to February 2000. Stork et al provide details of its specific aims and eligibility criteria.[17] Eligible patients met NCI SR-ALL criteria with either a B- or T-cell immunophenotype. This study enrolled 2,174 eligible patients. In CCG-1952, 106 patients were categorized as having T-ALL by the local institution, based on CD10, CD19, CD2, and CD7 immunophenotype. For the present analysis, the latter cases were re-evaluated by MB and LS, and 80 were classified as having T-ALL; the equivocal cases were excluded. At the end of a 3-drug induction with vincristine, prednisone, and native *E. coli* asparaginase, eligible patients were randomly assigned by the CCG central statistical office, using a 2×2 factorial design to one of four treatment regimens that compared intrathecal (IT) methotrexate (MTX) with IT MTX, cytarabine, hydrocortisone and oral mercaptopurine (MP) with thioguanine (TG), as previously reported.[18] Patients with unfavorable cytogenetics [$t(4;11)(q21;q23)$, $t(9;22)(q34;q11)$, and hypodiploidy (< 44 chromosomes)] were non-randomly assigned to an augmented regimen. In addition, patients were defined as having a slow early response (SER) if they did not achieve at least an M2 marrow status by day 14 of induction or M1 marrow by day 28 of induction, were also assigned to the augmented regimen. Details of therapy within each phase appear in Supplemental Table I. Only children with CNS-3 disease [CSF WBC $> 5/\mu\text{L}$ with positive cytomorphology] and/or testicular disease at diagnosis received irradiation during consolidation: 2,400 cGy cranial and 600 cGy spinal; or 2,400 cGy to both testes. Females were treated for 2 years and males for 3 years from the start of interim maintenance (IM). Of the 80 SR T-ALL patients enrolled on CCG-1952, 72 patients were randomized to one of the 4 regimens described above, 6 patients were non-randomly assigned to the augmented regimen, and 2 patients received only the induction phase of protocol therapy.

CCG-1991 opened in June 2000 and closed for T-ALL accrual in March 2004; it closed for patients with B-ALL in January 2005. Matloub et al detail the specific aims and eligibility

criteria[19]. Eligibility criteria for CCG-1991 and CCG-1952 were identical. Total number of eligible patients was 2,494, and 86 were identified as having T-ALL by local institutions, based on CD10, CD19, CD2, and CD7 immunophenotype. For the present analysis, these were reviewed by MB and YM. A 3-drug induction with dexamethasone, vincristine, and pegaspargase was followed by a 4-week consolidation phase of oral mercaptopurine and IT MTX. Eligible subjects were randomized in a 2×2 factorial design to four regimens comparing oral MTX with intravenous (IV) escalating-dose MTX in IM phases and a single course of delayed intensification (DI) with two DI phases, as previously reported.[19] As in CCG-1952, children with unfavorable cytogenetics at diagnosis [t(9;22)(q34;q11), t(4;11)(q21;q23), balanced t(1;19)(q23;p13) or hypodiploidy with < 45 chromosomes] were non-randomly assigned to an augmented regimen, as were those with SER. Based on early outcome data from CCG-1952, the definition of SER in CCG-1952 was modified for CCG-1991 to include subjects whose marrow status was M3 ($> 25\%$ lymphoblasts) at day 14 of induction, or M3 on day 7 and M2 on day 14 of induction, or those not in remission (M1) at day 28 of induction. Details of therapy within each phase appear in Supplemental Table II. Only children with CNS-3 disease and/or testicular disease received irradiation during consolidation: 1,800 cGy cranial irradiation or 2,400 cGy to both testes. Females were treated for 2 years and males for 3 years from the start of IM. Of the 86 patients with SR TALL enrolled on CCG-1991, 61 patients were randomized to one of the 4 regimens described above, 14 patients were non-randomly assigned to the augmented regimen, and 3 patients with CNS-3 disease were assigned to the OD regimen. The eight remaining patients did not receive protocol directed post-induction therapy.

POG-9404 enrolled patients between June 1996 and September 2001. Asselin et al provided details of its specific aims and eligibility criteria and protocol schema.[16] Patients were eligible if they were between 1 and 21 years of age, and diagnosed with T-ALL based on greater than 25% blasts in the marrow regardless of peripheral WBC. Patients with advanced stage lymphoblastic lymphoma were also eligible, but are not included in this report. T-cell immunophenotype was determined by local institutions with confirmation by flow cytometry at the POG central reference laboratory. Among patients with T-ALL, 84 met SR features for age and WBC. Prior to initiation of therapy, patients were randomized in a 2×2 factorial design to a standard regimen based on DFCI 87-01[15] to with or without dexrazoxane and with or without high-dose methotrexate (HD-MTX). In September 2000, early interim analysis of all patients found better EFS for patients treated with HD-MTX (72.2% vs 86%, $p = 0.002$); therefore, the MTX randomization, was closed to further accrual. Details of the therapy are outlined in Supplemental Table III. Central nervous system prophylaxis included cranial radiation (1,800 cGy) for all patients at week 22 of consolidation. Patients with CNS-2 (< 5 WBC/ μ l and positive cytomorphology) or CNS-3 (> 5 WBC/ μ l and positive cytomorphology) at diagnosis received two additional doses of intrathecal cytarabine and MTX during induction (day 8) and consolidation (week 16). All patients were treated for 2 years from the time of documented complete remission. Of the 84 patients with SR T-ALL enrolled on POG-9404, 69 were randomized among the 4 regimens and 15 non-randomly assigned to one of the two HD-MTX arms after September 2000.

Statistical methods

Study data for CCG 1952, CCG 1991, and POG 9404 were frozen as of 8 March 2008, 31 December 2010, and 26 September 2011, respectively. EFS times were calculated as time from study entry to first event (induction failure or death, relapse, second malignant neoplasm, or remission death) censored at date of last contact for patients who did not experience an event. Overall survival (OS) was calculated as time from study entry to time of death or date of last contact. Estimates for EFS and OS were calculated using the Kaplan-Meier method, and standard errors of the estimates were obtained by the Peto method.[20] The log-rank test was used to compare survival curves between groups. The chi-square test was used to compare proportions. Statistical significance was defined as a p-value less than 0.05. All analyses were performed using SAS® software. All graphics were generated using R (<http://www.R-project.org>, version 2.13.1).

Bone marrow evaluations

Local institutions determined bone marrow (BM) blast percentage on day 7 and day 14 aspirates, as was standard on CCG protocols.[21,22] Subjects with M3 (> 25% lymphoblasts) marrows at end of induction were removed from study. For patients on POG 9404, marrow aspirates were performed on day 22 to determine remission status; if not M1(< 5% lymphoblasts), they were repeated at day 43. Complete remission was defined as M1 marrow and no extramedullary disease at day 22 or 43 from start of therapy. Patients with M3 marrow on day 22, M2 (5–25% lymphoblasts) or M3 marrow on day 43, or histopathologically documented disease elsewhere on these dates were declared induction failures, and removed from study.

Relapse definitions

BM relapse was defined as an M3 marrow at any time after attaining remission at the end of induction, and occasionally, with approval from the study chair, as an M2 status with cytogenetic evidence of the diagnostic clone. Isolated CNS (iCNS) relapse occurred when CSF contained ≥ 5 WBC/ μ L and positive cytomorphology, without other sites of relapse. Combined relapses included those with simultaneous recurrence in BM and an extramedullary (EM) site.

Results

Patient characteristics

Presenting features of the patients with T-ALL and standard risk features are detailed according to treatment study in Table I.

Comparisons of Events and Outcomes

There were no statistically significant differences in 7-year EFS and OS for patients with SR T-ALL among the three clinical trials (Figures 1 and 2). The 7-year EFS was $74.1 \pm 5.8\%$ for CCG 1952; $81.8 \pm 5.3\%$ for CCG-1991; and $84.2 \pm 4.3\%$ for POG 9404. Overall survival was also comparable among the three studies: $86.1 \pm 4.6\%$ for CCG 1952; $88.3 \pm 4.4\%$ for CCG 1991; and $89.1 \pm 3.6\%$ for POG-9404. The difference in EFS and OS on

CCG-1952 (74.1% versus 86.1%) was greater than on CCG-1991 (81.8% versus 88.3%) and POG-9404 (84.2% v. 89.1%). Type and number of events are listed in Table II.

Despite the early outcome data that prompted closure of the non-HD-MTX regimens in favor of HD-MTX for all T-cell patients on POG-9404, 7-year EFS and OS were not statistically different between these two regimens for patients with SR T-ALL (EFS $84.4 \pm 5.4\%$ vs $83.9 \pm 6.9\%$; OS $90.3 \pm 4.4\%$ vs $87 \pm 6.3\%$).

Toxicity

Therapy was generally well tolerated in all three studies, with no unexpected toxicities aside from a high incidence of reversible and non-fatal sinusoidal obstruction syndrome among patients on the TG regimen of CCG-1952.[17,23] A direct comparison of toxicities among the three trials was not performed in this study, as various toxicities were collected and graded according to different matrices. Two deaths occurred during induction among patients with SR T-ALL: one in CCG-1991 from aspiration; and one in POG 9404 from hemorrhage. In POG 9404, mucositis was the only toxicity that occurred more frequently in the HD-MTX than the non-HD-MTX regimens.

Discussion

Children with T-ALL present with adverse prognostic features more commonly than do patients with pre B-ALL.[1,2,9–11] They also tend to display less favorable biological behavior with a slower reduction in minimal residual disease (MRD), an increased incidence of resistance to chemotherapy, a tendency for earlier relapse, and a higher incidence of CNS relapse.[12,24,25] Thus, T-ALL has generally been considered high-risk and treated with aggressive chemotherapy, often in association with CNS radiation therapy. Indeed, intensification of multimodal therapy has been successful in ameliorating the outcome of T-cell ALL in children.[4,24,26–30]

Strategies employed in the prognostic stratification and treatment of T-ALL have varied among the different childhood cancer consortia. In the 1980s, CCG defined the high-risk entity of Leukemia-Lymphoma Syndrome (L-LS), wherein patients met at least one of three clinical criteria (massive lymphadenopathy, massive splenomegaly, or large mediastinal mass) and at least one of three laboratory criteria (WBC $\geq 50,000/\mu\text{l}$, hemoglobin $\leq 10 \text{ g/dl}$, or E-rosette positive).[8] Patients with L-LS received intensified treatment, and approximately two-thirds probably had T-cell ALL. CCG abandoned prognostic stratification to L-LS in the mid 1990s in favor of NCI age and WBC risk criteria regardless of immunophenotype.[31] The BFM group previously stratified patients with T-ALL to either Medium Risk Group or Poor Risk Group depending on the leukemic cell mass estimate and the initial treatment response.[32,33] The DFCI treated patients with T-ALL and high-risk B-ALL on similar protocols.[12,34] St. Jude Total Therapy Programs stratified patients with T- and pre B-ALL according to identical criteria and treated them according to risk groups.[35–37]

POG-9404 provided more intensive therapy than the randomized regimens of CCG-1952 or 1991, including an anthracycline during induction, intensive post-induction with

anthracycline and asparaginase therapy, high-dose methotrexate (HD-MTX) for more than half of the patients, and 1,800 cGy of cranial irradiation. Important therapeutic differences between the CCG protocols and POG 9404 are highlighted in Table III. Notably the POG 9404 backbone included 2.4- to 4.8-fold higher cumulative anthracycline and 4- to 7-fold higher asparaginase doses than the CCG regimens, and cranial irradiation was given to 100% of POG-9404 patients as compared to none (CCG-1991) and 4% (CCG-1952) of the CCG patients. POG 9404 incorporated treatment strategies that had previously been shown efficacious in patients with T-ALL. In POG 8704 study for T-ALL and advanced lymphoblastic lymphoma, continuous complete remission rate was $68\% \pm 4\%$ for patients with T-ALL who received a high-dose intensive asparaginase regimen during consolidation ($25,000 \text{ IU/m}^2$ weekly for 20 weeks) versus $55\% \pm 4\%$, $p = 0.002$ for those who did not.[38] Similar to most high-risk protocols, anthracyclines were given in both induction and post induction on POG-9404. HD-MTX randomization was based on results of the DFCI and BFM protocols.

The POG 9404 regimen did not include the 8-week DI phases given in CCG 1952 and 1991. Regimens incorporating one or two DI phases were standard across risk groups in CCG ALL Phase III trials starting in the late 1980s, after they were shown to improve outcome in CCG-105 and 106.[17,19,39–43] The CCG-1952 trial was designed with two DI phases, informed by early outcomes of a prior randomized trial.[41] With dexamethasone substituting for prednisone in induction and maintenance in CCG-1991, the benefit of a second DI was re-evaluated, and outcomes with one or two DI phases were found to be equivalent.[19]

On CCG 1952 and 1991, patients with SER were non-randomly assigned to intensified treatment, which included significantly more anthracycline, cyclophosphamide, and asparaginase. On CCG-1952, 7.7% of patients with T-ALL met SER criteria; on CCG 1991, 18% met that study's broadened definition of SER. Despite intensified therapy, patients with T-ALL and SER on CCG 1952 did much worse than those with T-ALL and rapid early response (RER), with only 25% 7-year OS compared to 91% OS. Patients with T-ALL and SER on CCG-1991 also experienced outcomes inferior to their counterparts with RER, with 70% 7-year OS compared with 92% OS. POG 9404 did not address rapidity of response; thus, EFS and OS of an SER subset on that study is unknown. In our present analyses, patients with SR T-ALL and RER on CCG-1991 had EFS equivalent to SR T-ALL patients treated with more intensive POG 9404 therapy. However, without rapidity of response data from POG-9404, we cannot compare EFS and OS of patients with SR T-ALL and RER between these two studies.

The outcomes for cohorts with SR T-ALL on the CCG studies 1952 and 1991 were inferior to those of their concurrent counterparts with SR B-ALL, wherein a large fraction of these patients had favorable cytogenetics.[17,19]

In early 2004, the COG data monitoring committee performed an interim analysis and estimated the 2-year EFS for patients with T-ALL on CCG-1991 to be 82–85%. This outcome was determined to be unacceptably low compared to similar patients on POG-9404 with 2-year EFS of 89%. Thus, CCG-1991 was closed to patients with T-ALL in favor of a

more intensive treatment strategy, and COG determined that patients with SR T-ALL would no longer be eligible for SR-ALL protocols. However, with longer follow-up comparing 7-year EFS and OS, no difference in outcome is found between CCG-1991 and POG-9404 for patients with SR-T-ALL, but both show lower EFS and OS rates than obtained for patients with SR B-ALL on the recent COG AALL0331 trial[44] and for patients with T-ALL on the recent COG AALL0434 trial.[45]

This report demonstrates that the 7-year EFS and OS are not statistically different among patients with SR T-ALL treated on the three clinical trials, despite EFS being 10% and 7% lower on CCG 1952 compared to POG 9404 and CCG 1991 respectively. The 7-year OS was equivalent among the three studies. The larger difference in EFS and OS on CCG-1952 than on CCG-1991 and POG-9404 suggests that the events on the former study were more salvageable than on the other two. Indeed, the difference in type of events among the studies, which included more iCNS relapses and fewer induction and remission deaths on CCG-1952 may explain these results. It is also possible that second remission was harder to attain following relapse on the more intensive POG-9404 than the CCG studies. Based on these excellent outcomes, the recently closed COG T-cell study, AALL0434, omitted cranial irradiation for patients who were NCI SR by age and WBC, with CNS-I status, no testicular involvement, an M1 marrow by day-15 induction and MRD <0.1% at end of induction. Patients were randomized after induction to regimens similar in design and intensity to COG HR B-ALL protocols.[45]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Acknowledgement: This work was supported by COG Chair's Grant U10 CA98543 and U10CA180886, COG Statistics and Data Center grants U10 CA098413 and U10CA180899, and Support for Human Specimen Banking U24CA114766.

The authors express gratitude to all the patients and families who participated in this trial. We also wish to thank the COG staff, institutional investigators and their clinical research staff involved in these trials. YM is the Angie Fowler Chair of Adolescent & Young Adult Cancer and LCS is the Robert Neerhout Professor of Pediatrics.

ABBREVIATIONS

B-ALL	Precursor-B ALL
BFM	Berlin-Frankfurt-Munster
CCG	Children Cancer Group
CNS	Central nervous system
DFCI	Dana-Farber Cancer Institute
EFS	Event-free-survival
HD-MTX	High-dose methotrexate

iCNS	Isolated central nervous system relapse
IT	Intrathecal
IV	Intravenous
MP	Mercaptopurine
MRD	Minimal residual disease
MTX	Methotrexate
NCI	National Cancer Institute
OS	Overall survival
POG	Pediatric Oncology Group
RER	Rapid early response
SER	Slow early response
SR	Standard-risk
T-ALL	T-lineage acute lymphoblastic leukemia
TG	Thioguanine
WBC	White blood cell count

References

1. Pullen DJ, Falletta JM, Crist WM, Vogler LB, Dowell B, Humphrey GB, Blackstock R, Eys JV, Cooper MD, Metzgar RS, Meydrech EF. Southwest Oncology Group experience with immunological phenotyping in acute lymphocytic leukemia of childhood. *Cancer research*. 1981; 41(11 Pt 2):4802–4809. [PubMed: 6975163]
2. Pullen DJ, Boyett JM, Crist WM, Falletta JM, Roper M, Dowell B, Van Eys J, Jackson JF, Humphrey GB, Metzgar RS, Cooper MD. Pediatric oncology group utilization of immunologic markers in the designation of acute lymphocytic leukemia subgroups: influence on treatment response. *Ann N Y Acad Sci*. 1984; 428:26–48. [PubMed: 6234834]
3. Borowitz MJ.; Dowell, BL.; Boyett, JM.; Pullen, DJ.; Crist, WM.; Qudus, FM.; Falletta, JM.; Metzgar, RS. Clinicopathologic aspects of E rosette negative T cell acute lymphocytic leukemia: a Pediatric Oncology Group study. 1986.
4. Uckun F, Reaman G, Steinherz P, Arthur D, Sather H, Trigg M, Tubergen D, Gaynon P. Improved outcome for children with T-lineage acute lymphoblastic leukemia after contemporary chemotherapy: a Children's Cancer Group study. *Leuk Lymphoma*. 1996; 24:57–70. [PubMed: 9049962]
5. Shuster JJ, Falletta JM, Pullen DJ, Crist WM, Humphrey GB, Dowell BL, Wharam MD, Borowitz M. Prognostic factors in childhood T-cell acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood*. 1990; 75(1):166–173. [PubMed: 1688495]
6. Crist WM, Shuster JJ, Falletta J, Pullen DJ, Berard CW, Vietti TJ, Alvarado CS, Roper MA, Prasthofer E, Grossi CE. Clinical features and outcome in childhood T-cell leukemia-lymphoma according to stage of thymocyte differentiation: a Pediatric Oncology Group Study. *Blood*. 1988; 72(6):1891–1897. [PubMed: 3058229]
7. Conter V, Schrappe M, Arico M, Reiter A, Rizzari C, Dordelmann M, Valsecchi MG, Zimmermann M, Ludwig WD, Basso G, Masera G, Riehm H. Role of cranial radiotherapy for childhood T-cell acute lymphoblastic leukemia with high WBC count and good response to prednisone. *Associazione*

- Italiana Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Munster groups. *Journal Of Clinical Oncology*. 1997; 15(8):2786–2791. [PubMed: 9256120]
8. Steinherz PG, Gaynon PS, Breneman JC, Cherlow JM, Grossman NJ, Kersey JH, Johnstone HS, Sather HN, Trigg ME, Uckun FM, Bleyer WA. Treatment of patients with acute lymphoblastic leukemia with bulky extramedullary disease and T-cell phenotype or other poor prognostic features: randomized controlled trial from the Children's Cancer Group. *Cancer*. 1998; 82(3):600–612. [PubMed: 9452280]
  9. Kersey JH, LeBien TW, Hurwitz R, Nesbit ME, Gajl-Peczalska KJ, Hammond D, Miller DR, Coccia PF, Leikin S. Childhood leukemia-lymphoma. Heterogeneity of phenotypes and prognoses. *American Journal of Clinical Pathology*. 1979; 72(4 Suppl):746–752. [PubMed: 291337]
  10. Sallan SE, Ritz J, Pesando J, Gelber R, O'Brien C, Hitchcock S, Coral F, Schlossman SF. Cell surface antigens: prognostic implications in childhood acute lymphoblastic leukemia. *Blood*. 1980; 55(3):395–402. [PubMed: 6986918]
  11. Greaves MF, Janossy G, Peto J, Kay H. Immunologically defined subclasses of acute lymphoblastic leukaemia in children: their relationship to presentation features and prognosis. *British journal of haematology*. 1981; 48(2):179–197. [PubMed: 7016165]
  12. Goldberg JM, Silverman LB, Levy DE, Dalton VK, Gelber RD, Lehmann L, Cohen HJ, Sallan SE, Asselin BL. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. *Journal of Clinical Oncology*. 2003; 21(19):3616–3622. [PubMed: 14512392]
  13. Arico M, Valsecchi MG, Conter V, Rizzari C, Pession A, Messina C, Barisone E, Poggi V, De Rossi G, Locatelli F, Micalizzi MC, Basso G, Masera G. Improved outcome in high-risk childhood acute lymphoblastic leukemia defined by prednisone-poor response treated with double Berlin-Frankfurt-Muenster protocol II. *Blood*. 2002; 100(2):420–426. [PubMed: 12091331]
  14. Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, Gelber R, Heerema N, Korn EL, Link M, Murphy S, Pui CH, Pullen J, Reamon G, Sallan SE, Sather H, Shuster J, Simon R, Trigg M, Tubergen D, Uckun F, Ungerleider R. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia [see comments]. *J Clin Oncol*. 1996; 14(1):18–24. [PubMed: 8558195]
  15. Goldberg JM, Silverman LB, Levy DE, Dalton VK, Gelber RD, Lehmann L, Cohen HJ, Sallan SE, Asselin BL. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. *J Clin Oncol*. 2003; 21(19):3616–3622. [PubMed: 14512392]
  16. Asselin BL, Devidas M, Wang C, Pullen J, Borowitz MJ, Hutchison R, Lipshultz SE, Camitta BM. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood*. 2011; 118(4):874–883. [PubMed: 21474675]
  17. Stork LC, Matloub Y, Broxson E, La M, Yanofsky R, Sather H, Hutchinson R, Heerema NA, Sorrell AD, Masterson M, Bleyer A, Gaynon PS. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children's Oncology Group CCG-1952 clinical trial. *Blood*. 2010; 115(14):2740–2748. [PubMed: 20124218]
  18. Matloub Y, Lindemulder S, Gaynon PS, Sather H, La M, Broxson E, Yanofsky R, Hutchinson R, Heerema NA, Nachman J, Blake M, Wells LM, Sorrell AD, Masterson M, Kelleher JF, Stork LC. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood*. 2006; 108(4):1165–1173. [PubMed: 16609069]
  19. Matloub Y, Bostrom BC, Hunger SP, Stork LC, Angiolillo A, Sather H, La M, Gastier-Foster JM, Heerema NA, Sailer S, Buckley PJ, Thomson B, Cole C, Nachman JB, Reaman G, Winick N, Carroll WL, Devidas M, Gaynon PS. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2011; 118(2):243–251. [PubMed: 21562038]

20. Peto R, Pike MC, Armitage P, Breslow N, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, II. Analysis and examples. *Br J Cancer*. 1977; 35:1–39. [PubMed: 831755]
21. Miller DR, Coccia PF, Bleyer WA, Lukens JN, Siegel SE, Sather HN, Hammond GD. Early Response to Induction Therapy As a Predictor of Disease-Free Survival and Late Recurrence of Childhood Acute Lymphoblastic Leukemia: a Report From the Childrens Cancer Study Group. *Journal Of Clinical Oncology*. 1989; 7(12):1807–1815. [PubMed: 2685179]
22. Heerema N, Sather H, Reaman G, Hutchinson R, Lange B, Nachman J, Steinherz P, Uckun F, Gaynon P, Trigg M, Arthur D. Cytogenetic studies of acute lymphoblastic leukemia: clinical correlations results from the Children's Cancer Group. *J Assoc Genetic Technol*. 1998; 24:206–212.
23. Broxson EH, Dole M, RW, Laya BF, Stork L. Portal hypertension (PH) develops in a subset of children treated with maintenance oral 6- thioguanine for standard risk acute lymphoblastic leukemia. *Blood*. 2001; 98(11):113a.
24. Schrappe M, Reiter A, Ludwig W-D, Harbott J, Zimmerman M, Hiddeman W, Niemayer C, Henze G, Felges A, Zintl F, Kornhuber B, Ritt J, Welte K, Gadner H, Riehm H. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial irradiation: results of trial ALL-BFM 90. *Blood*. 2000; 95(11):3310–3322. [PubMed: 10828010]
25. Crist W, Shuster J, Look T, Borowitz M, Behm F, Bowman P, Frankel L, Pullen J, Krance R, Steuber P. Current results of studies of immunophenotype-, age- and leukocyte-based therapy for children with acute lymphoblastic leukemia. The Pediatric Oncology Group. *Leukemia*. 1992; 6 (Suppl 2):162–166. [PubMed: 1578922]
26. Steinherz PG, Gaynon P, Miller DR, Reaman G, Bleyer A, Finklestein J, Evans RG, Meyers P, Steinherz LJ, Sather H, Hammond D. Improved disease-free survival of children with acute lymphoblastic leukemia at high risk for early relapse with the New York regimen--a new intensive therapy protocol: a report from the Childrens Cancer Study Group. *J Clin Oncol*. 1986; 4(5):744–752. [PubMed: 3517244]
27. Schorin MA, Blattner S, Gelber RD, Tarbell NJ, Donnelly M, Dalton V, Cohen HJ, Sallan SE. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber Cancer Institute/Children's Hospital Acute Lymphoblastic Leukemia Consortium Protocol 85-01. *J Clin Oncol*. 1994; 12(4):740–747. [PubMed: 8151317]
28. Clavell LA, Gelber RD, Cohen HJ, Hitchcock Bryan S, Cassady JR, Tarbell NJ, Blattner SR, Tantravahi R, Leavitt P, Sallan SE. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. *N Engl J Med*. 1986; 315(11):657–663. [PubMed: 2943992]
29. Schrappe M, Valsecchi MG, Bartram CR, Schrauder A, Panzer-Grumayer R, Moricke A, Parasole R, Zimmermann M, Dworzak M, Buldini B, Reiter A, Basso G, Klingebiel T, Messina C, Ratei R, Cazzaniga G, Koehler R, Locatelli F, Schafer BW, Arico M, Welte K, van Dongen JJ, Gadner H, Biondi A, Conter V. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. *Blood*. 2011; 118(8):2077–2084. [PubMed: 21719599]
30. Willemse MJ, Seriu T, Hettinger K, d'Aniello E, Hop WC, Panzer-Grumayer ER, Biondi A, Schrappe M, Kamps WA, Masera G, Gadner H, Riehm H, Bartram CR, van Dongen JJ. Detection of minimal residual disease identifies differences in treatment response between T-ALL and precursor B-ALL. *Blood*. 2002; 99(12):4386–4393. [PubMed: 12036866]
31. Gaynon PS, Angiolillo AL, Carroll WL, Nachman JB, Trigg ME, Sather HN, Hunger SP, Devidas M. Children's Oncology G. Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983–2002: a Children's Oncology Group Report. *Leukemia*. 2010; 24(2):285–297. [PubMed: 20016531]
32. Reiter A, Schrappe M, Ludwig WD, Hiddemann W, Sauter S, Henze G, Zimmermann M, Lampert F, Havers W, Niethammer D, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. *Blood*. 1994; 84(9):3122–3133. [PubMed: 7949185]
33. Moricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, Ludwig WD, Ritter J, Harbott J, Mann G, Klingebiel T, Zintl F, Niemeyer C, Kremens B, Niggli F, Niethammer D,

- Welte K, Stanulla M, Odenwald E, Riehm H, Schrappe M. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia*. 2010; 24(2):265–284. [PubMed: 20010625]
34. Silverman LB, Stevenson KE, O'Brien JE, Asselin BL, Barr RD, Clavell L, Cole PD, Kelly KM, Laverdiere C, Michon B, Schorin MA, Schwartz CL, O'Holleran EW, Neuberg DS, Cohen HJ, Sallan SE. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985–2000). *Leukemia*. 2010; 24(2):320–334. [PubMed: 20016537]
  35. Rivera GK, Raimondi SC, Hancock ML, Behm FG, Pui CH, Abromowitch M, Mirro J Jr, Ochs JS, Look AT, Williams DL, Murphy S, Dahl G, Kalwinsky D, Evans W, Kun L, Simone J, Crist W. Improved outcome in childhood acute lymphoblastic leukaemia with reinforced early treatment and rotational combination chemotherapy. *Lancet*. 1991; 337(8733):61–66. [PubMed: 1670723]
  36. Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *New England Journal of Medicine*. 1998; 338(8):499–505. [PubMed: 9468466]
  37. Pui CH, Sandlund JT, Pei D, Campana D, Rivera GK, Ribeiro RC, Rubnitz JE, Razzouk BI, Howard SC, Hudson MM, Cheng C, Kun LE, Raimondi SC, Behm FG, Downing JR, Relling MV, Evans WE. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIIB at St Jude Children's Research Hospital. *Blood*. 2004; 104(9):2690–2696. [PubMed: 15251979]
  38. Amylon MD, Shuster J, Pullen J, Berard C, Link MP, Wharam M, Katz J, Yu A, Laver J, Ravindranath Y, Kurtzberg J, Desai S, Camitta B, Murphy SB. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. *Leukemia*. 1999; 13(3):335–342. [PubMed: 10086723]
  39. Tubergen D, Gilchrist G, O'Brien A, Coccoa P, Sather H, Waskerwitz M, Hammond D. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features. *J Clin Oncol*. 1993; 11:527–537. [PubMed: 8445428]
  40. Gaynon PS, Steinherz PG, Bleyer WA, Ablin AR, Albo VC, Finklestein JZ, Grossman NJ, Novak LJ, Pyesmany AF, Reaman GH, Chappell RJ, Sather H, Hammond D. Improved therapy for children with acute lymphoblastic leukemia and unfavorable presenting features: a follow-up report of the Children's Cancer Group Study CCG-106. *J Clin Oncol*. 1993; 11(11):2234–2242. [PubMed: 8229139]
  41. Lange BJ, Bostrom BC, Cherlow JM, Sensel MG, La MK, Rackoff W, Heerema NA, Wimmer RS, Trigg ME, Sather HN. Double-delayed intensification improves event-free survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2002; 99(3):825–833. [PubMed: 11806983]
  42. Bostrom BC, Sensel MR, Sather HN, Gaynon P, La MK, Johnston K, Erdmann GR, Gold S, Heerema NA, Hutchinson RJ, Provisor AJ, Trigg ME. 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]
  43. Seibel NL, Steinherz PG, Sather HN, Nachman JB, Delaat C, Ettinger LJ, Freyer DR, Mattano LA Jr, Hastings CA, Rubin CM, Bertolone K, Franklin JL, Heerema NA, Mitchell TL, Pyesmany AF, La MK, Edens C, Gaynon PS. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2008; 111(5):2548–2555. [PubMed: 18039957]
  44. Mattano LA Jr, Devidas M, Friedmann AM, Raetz E, Loh M, Buckley P, Borowitz MJ, Carroll AJ, Gastier-Foster J, Heerema NA, Kadan-Lottick N, Matloub Y, Marshall DT, Stork LC, Wood BL, Winick NJ, Hunger P, Carroll WL, Maloney K. Outstanding Outcome for Children with Standard Risk-Low (SR-Low) Acute Lymphoblastic Leukemia (ALL) and No Benefit to Intensified Peg-Asparaginase (PEG-ASNase) Therapy: Results of Children's Oncology Group (COG) Study AALL0331. *Blood*. 2014; 124(21):793.
  45. Wood BL, Winter SS, Dunsmore KP, Devidas M, Chen S, Asselin A, Esiashvili N, Loh ML, Winick NJ, Carroll WL, Raetz EA, Hunger SP. T-Lymphoblastic Leukemia (T-ALL) Shows

Excellent Outcome, Lack of Significance of the Early Thymic Precursor (ETP) Immunophenotype, and Validation of the Prognostic Value of End-Induction Minimal Residual Disease (MRD) in Children's Oncology Group (COG) Study AALL0434. *Blood*. 2014; 124(21)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

EFS for SR T-ALL patients treated on CCG 1952, CCG 1991, and POG 9404. Total of 10 patients were excluded from EFS analyses: 2 patients on CCG 1952 did not receive a protocol regimen; 8 on CCG 1991 were excluded for the same reason. 7-year EFS: CCG 1952: $74.1 \pm 5.8\%$; CCG-1991: $81.8 \pm 5.3\%$; POG 9404: $84.2 \pm 4.3\%$.

Figure 2.

OS for SR T-ALL patients treated on CCG 1952, CCG 1991 and POG 9404. Total of 10 patients were excluded from OS analyses: 2 patients on CCG 1952 did not receive a protocol regimen; 8 on CCG 1991 were excluded for the same reason. 7-year OS: CCG-1952: $86.1 \pm 4.6\%$; CCG 1991: $88.3 \pm 4.4\%$; POG 9404: $89.1 \pm 3.6\%$.

Table I

Presenting features and end-of-induction status of SR T-ALL

	1952 n (%)	1991 n (%)	9404 n (%)	<i>P</i>
Age (years)				
< 2	6 (7.5)	6 (7)	4 (4.8)	0.2806
2–5	39 (48.8)	41 (47.7)	30 (35.7)	
6–9	35 (43.8)	39 (45.4)	50 (59.5)	
SEX				
F	26 (32.5)	32 (37.2)	28 (33.3)	0.7901
M	54 (67.5)	54 (62.8)	56 (66.7)	
WBC				
< 20K	59 (73.8)	49 (57)	46 (54.8)	0.0244
≥ 20K	21 (26.3)	37 (43)	38 (45.2)	
EM* Disease^{a,b}				
Testicular	0	0	2 (2.4)	----
CNS-1	55 (68.8)	60 (78.9)	68 (81)	0.1162 ^c
CNS-2	8 (10)	3 (3.9)	9 (10.7)	
CNS-3	3 (3.8)	0 (0)	6 (7.1)	
TLP+	2 (2.5)	4 (5.3)	----	
TLP-	10 (12.5)	9 (11.8)	----	
Splenomegaly	38 (47.5)	42 (48.8)	16 (19.1)	<0.0001
Mediastinal mass	27 (33.8)	29 (33.7)	53 (63.1)	<0.0001
DS[@]	0	3 (3.5)	0	----
End-of-induction BM				
M1 [^]	75 (93.8)	79 (96.3)	81 (96.4)	0.4514
M2 [^] &M3 [^]	5 (6.3)	3 (3.7)	2 (2.4)	

* Extramedullary

^a Testicular status unknown for 2 patients on POG 9404^b CNS status unknown for 2 patients on CCG 1952 and for 10 patients on CCG 1991^c p-value based on comparison only of CNS (1,2,3) across all three studies[@] Patients with Down Syndrome[^] See text for definitions

Table II

Type and number of events in the different studies

	CCG-1952	CCG-1991	POG-9404
Induction Failure *	0	1	2
iBM @	10	6	3
iCNS &	7	4	1
BM + CNS	1	0	0
Testicular	0	0	1
Other EM ^	3	3	2
Death as first event	0	3	2
SMN	1	0	2
TOTAL	22	17	13

* Failure to achieve M1 status at the end of induction

@ Isolated bone marrow relapse

& Isolated central nervous system relapse

^ Extramedullary site relapse

Table III

Main differences in therapy among the three studies *

	CCG 1952	CCG-1991	POG 9404
HD MTX**	None	None	5 gm/m ² X 4 (in half the subjects)
Doxurubicin	150 mg/m ²	75 or 150 mg/m ²	360 mg/m ²
Asparaginase	6,000 [^] U/m ² x 21 doses	PEG ^{^^} 2,500 U/m ² x 2–3 doses	25,000 [^] U/m ² x 20 doses
Vincristine	49.5 – 67.5 mg/m ²	40.5 – 76.5 mg/m ²	74 mg/m ²
Cranial Irradiation	CNS-3 ONLY 1800 cGy cranial and 600 cGy spinal	CNS-3 ONLY 1800 cGy	All patients 1800 cGy
Duration of Therapy	2–3 years [#]	2–3 years [#]	2 years

* Please refer to separate tables for detailed comparisons

** High-dose methotrexate

[^] Native E. coli preparation^{^^} Pegylated preparation[#] 2 years for females, 3 years for males from the start of IM