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Long Term Results of the Children's Cancer Group Studies for Childhood Acute Lymphoblastic Leukemia 1983–2002: a Children's Oncology Group Report

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Abstract

The Children's Cancer Group enrolled 13,298 young people age < 21 years on one of 16 protocols between 1983 and 2002. Outcomes were examined in three time periods, 1983–1988, 1989–1995, 1996–2002. Over the three intervals, 10-year event-free survival (EFS) for Rome/NCI standard risk and higher risk B-precursor patients was 68% and 58%, 77% and 63%, and 78% and 67%, respectively; while for standard risk and higher risk T-cell patients, EFS was 65% and 56%, 78% and 68%, and 70% and 72%, respectively. Five-year EFS for infants was 36%, 38%, and 43%, respectively. Seminal randomized studies led to a number of important findings. Stronger post induction intensification improved outcome for both standard and higher risk patients. With improved systemic therapy, additional IT methotrexate effectively replaced cranial radiation. For standard risk patients receiving three-drug induction, iso-toxic substitution of dexamethasone for

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prednisone improved EFS. Pegylated asparaginase safely and effectively replaced native asparaginase. Thus, rational therapy modifications yielded better outcomes for both standard and higher risk patients. These trials provide the platforms for current Children's Oncology Group trials.

Keywords

Acute lymphoblastic leukemia; children; randomized clinical trials

Introduction

Children's Oncology Group (COG) member institutions care for the majority of infants, children, and adolescents with Acute Lymphoblastic Leukemia in North America and Oceania. Work by the legacy Children's Cancer Group (CCG), dating back more than 40 years, serves as the foundation for many current COG trials. Studies prior to 1983 built on the pioneering work of Donald Pinkel and his colleagues at St. Jude Children's Research Hospital,(1) and introduced Berlin Frankfurt Münster (BFM)-based post induction intensification (Protocol Ib or Consolidation and Protocol II or Delayed Intensification (DI), (2) and a widely-used age-based dosing schedule for IT (IT) therapy.(3) The prognostic significance of early marrow response, assessed by marrow blast percentage 7 and 14 days into induction, was defined. (4) Event-free survival (EFS) improved with vincristine and prednisone pulses as the sole post-induction intensification and extended maintenance IT methotrexate replaced pre-symptomatic whole brain irradiation for lowest risk patients.(5)

Thirteen trials, conducted from 1983 through 1995 were summarized in the December 2000 issue of Leukemia. (6) Two 1983–1988 studies (100 series), namely, CCG-106 (7) and CCG-123, (8) proved the advantage of early BFM-based strategies, prior to the introduction of BFM protocol M or methotrexate 5 g/m^2, over previous CCG efforts for higher risk (HR) children. A third study, CCG-105, showed that more effective systemic therapy and extended IT methotrexate could spare all CNS negative standard risk (SR) children from whole brain irradiation and proved the value of post induction intensification.(9, 10) Induction anthracycline, higher dose induction prednisone, and intensive consolidation added no further benefit for standard risk patients receiving DI and vincristine-prednisone pulses in maintenance. The 1989–1995 studies (1800 series) further restricted whole brain irradiation (11) and showed the value of longer and stronger post-induction intensification, the so-called "Augmented BFM" regimen for HR patients (12) and dexamethasone for SR patients. (13) Patients received monthly vincristine and prednisone or dexamethasone pulses through maintenance in all of these trials, unlike contemporary BFM practice.

This report provides further follow-up on past 1983–1995 studies, and adds 4 additional trials and 3482 additional patients from 1996–2002 (1900 series). Replacement of 6-mercaptopurine (6MP) with 6-thioguanine (6TG) provided an EFS advantage but with unacceptable liver toxicity for SR patients on CCG-1952.(14) IT triple therapy, i.e., cytarabine, methotrexate, and hydrocortisone, halved CNS relapse rates compared to IT methotrexate alone but allowed excess marrow and testes relapses on a methotrexate-poor

platform, resulting in an inferior survival.(15) CCG-1962 showed that pegylated asparaginase safely and effectively replaced native asparaginase.(16) CCG-1961 explored the components of the Augmented "BFM" regimen for higher risk patients with a rapid Day 7 response and showed the advantage for stronger, not longer post induction intensification. (17) This report excludes the final CCG trial, CCG-1991, which completed accrual only in 2005.(18, 19)

Materials and Methods

The Clinical Trials Evaluation Panel of the National Cancer Institute of the United States approved all protocols. Local Institutional Review Board approval and written individual/parental informed consent were required. Details of all studies have been published.

Between 1983 and 2002, 13,298 infants, children, and adolescents, age < 21 years at diagnosis enrolled on one of 16 treatment protocol. The diagnosis of ALL was based on morphology,(20) histochemistry, and increasingly on flow cytometry. Patients with FAB L3 morphology and myeloperoxidase positivity were excluded.

Between 1983 and 1988, a total of 3713 eligible, evaluable patients were entered on the CCG-100 series studies. Patients were stratified by age, white blood cell count (WBC), gender, platelet count, FAB classification,(21) and lymphomatous features.(22) The 'lowest risk' patients received vincristine, prednisone, and L-asparaginase during induction, IT methotrexate in induction, consolidation, and maintenance, and daily oral 6MP, weekly oral methotrexate, and monthly vincristine/prednisone pulses in maintenance on CCG-104. With a 2×2×2 factorial design, 'intermediate risk' patients were randomly allocated to receive standard or intensive induction/consolidation, DI or no intensification, and 18 Gy cranial irradiation or every 12 week IT methotrexate on CCG-105.(9, 10) A small number of intermediate risk patients were enrolled on CCG-139 and received either intermediate dose methotrexate 0.5 g/m2 with leucovorin rescue or oral methotrexate. No patient received DI. (23) 'Higher risk' patients with lymphomatous features were randomly allocated to LSA2L2 with or without cranial irradiation, the New York (NY) I regimen, or the CCG modified BFM regimen on CCG-123.(8) 'Higher risk' patients without lymphomatous features were randomly allocated to the standard CCG regimen, NY I regimen, or the CCG-modified BFM regimen on CCG-106.(7) Infants were treated on CCG-107, which employed very high-dose methotrexate (33.6 g/m2) with leucovorin rescue. (24)

Between 1989 and 1995, a total of 5121 eligible, evaluable patients were entered on the CCG-1800 series studies. Age, WBC, gender, platelet count, and lymphomatous features stratified patients. 'Lowest risk' patients were randomly allocated to receive DI or not on CCG-1881. (25) 'Intermediate risk patients,' now excluding anyone 10 years of age or older, all received prednisone in induction and a single DI phase and were randomly allocated to receive or not a second DI phase and vincristine/prednisone pulses every 3 or 4 weeks on CCG-1891.(26) Upon completion of these initial studies in 1992 and 1993, subsequent SR patients(27) were enrolled on CCG-1922, which compared oral vs parenteral 6MP and dexamethasone vs prednisone in induction and maintenance. All patients received dexamethasone during a single DI phase and IT methotrexate every 12 weeks in

maintenance. (13) Cranial irradiation was reserved for those with overt CNS disease at diagnosis. 'Higher risk' patients with lymphomatous features were randomly allocated to NYI or NYII therapy on CCG-1901. All received cranial irradiation. (28) 'Higher risk' patients with WBC ≥50,000/μl or age ≥10 years who lacked lymphomatous features were assigned to CCG-1882. On CCG-1882, patients with no CNS disease at diagnosis (<5 leukocytes/μl or no blasts in the cerebrospinal fluid) and <25% marrow blasts on day 7 of an induction phase consisting of vincristine, prednisone, L-asparaginase, and daunorubicin (rapid early responders, RER) were randomly allocated to receive 18 Gy cranial irradiation or additional IT methotrexate.(11) Patients on CCG-1882 with >25% marrow blasts on day 7 of induction (slow early responders, SER) were initially treated on a pilot study of longer and stronger post induction intensification, the "Augmented BFM regimen." After an initial cohort demonstrated the safety of this regimen, SER patients were randomly allocated to our standard CCG-modified BFM regimen or to the Augmented BFM regimen.(12) Infants <1 year of age, were treated on CCG-1883 and received intensive induction, consolidation including very high-dose methotrexate (33.6 g/m2), and intensive post-consolidation therapy without cranial irradiation.(24) Classification as B-precursor and T-lineage was determined centrally. FAB L2 morphology no longer contributed to treatment allocation. Cytogenetic diagnosis was obtained locally but reviewed centrally.

Between 1996 and 2002, 4464 eligible, evaluable patients were enrolled on the CCG-1900 series studies. Treatment was allocated by age, WBC, and Day 7 or 14 marrow response. Specifically, T-cell patients who met SR age and WBC criteria were now classified as SR. On CCG-1952, SR patients received three drug – vincristine, prednisone, and native e. coli asparaginase induction, two 2-month DI phases, and daily oral 6MP, weekly oral methotrexate, every 4 week vincristine/prednisone pulses, and every 12 week IT therapy. (14, 15) All patients received IT cytarabine at the start of treatment, IT methotrexate in induction and 6TG in DI. Patients were randomly assigned to receive IT methotrexate or IT triple therapy after induction and to receive either 6TG or 6MP in consolidation, interim maintenance, and maintenance. SR patients with marrow blasts > 25% on Day 14 of induction received the Augmented BFM regimen after induction. A small number of SR patients were enrolled on CCG-1962. Patients were randomized to receive native (21 doses) or pegylated (3 doses) asparaginase. All received three-drug induction (with prednisone) and two DI phases. (16) On CCG-1961, HR RER patients were randomly assigned to receive standard or longer duration and standard or stronger intensity post induction intensification. HR SER patients received the Augmented BFM regimen and were randomly assigned to either weekly doxorubicin or sequential idarubicin/cyclophosphamide in each of two DI phases. (17) At the start of the study, B-precursor SER patients were randomly assigned to receive or not to receive B43-PAP, an anti-CD19 pokeweed antiviral protein immunotoxin. However, the manufacturer withdrew the drug from study. (29) Infants, <1 year of age, were treated on CCG-1953 (30) with an intensive "triple induction" strategy shared with POG 9407 (31, 32) and received intensive induction, consolidation including high-dose methotrexate (5 g/m^2), and intensive post-consolidation therapy with no cranial irradiation. Classification as B-precursor and T-lineage was determined at a central reference laboratory. Cytogenetic diagnosis was obtained locally but reviewed centrally.

Statistical Considerations

EFS time was defined as the time from diagnosis to first event (induction failure, relapse, death, or second malignant neoplasm) or last contact for those who did not have an event. Overall survival (OS) time was defined as time from diagnosis to death or last contact. Event-free survival and OS rates were computed by the method of Kaplan-Meier (33) and were compared using the log-rank test. Cox proportional hazards regression was used to identify independent prognostic factors for EFS. For patients who achieved complete remission, cumulative incidence rates of isolated CNS or any (isolated plus combined) CNS relapse, therapy-related second malignancies, and remission deaths, were computed and compared using Gray's method (34) adjusting for competing events. Data for the various studies frozen as of 03/28/2008 were used in the analyses.

Results

Table 1 summarizes the 21 randomized questions posed in the twelve studies that posed a randomized question.

In all three periods, patients with marrow blasts ≥ 25% at the end of induction were removed from protocol therapy as induction failures (an event) and may have later undergone allogeneic stem cell transplantation. The CCG-100 series (1983–1988) and CCG-1800 series (1989–1995) studies made no specific allowance for first remission transplantation. The CCG-1921 study, 1993–1996, captured 29 patients receiving first remission transplant. Patients with t(4;11), t(9;22), hypodiploidy (chromosomes ≤ 44) or induction failure were eligible. In addition, infants (2–12 months) with CD10 negativity, presenting WBC ≥ 100,000/μl or Day 14 marrow blasts > 5% and older children, age ≥ 10 years, with presenting WBC ≥ 200,000/μl were also eligible. (35) On the CCG-1900 series (1996–2002), patients with t(4;11), t(9;22), hypodiploidy < 44 chromosomes, or marrow blasts between 5% and 25% at the end of induction were eligible for allogeneic transplant, if a suitable donor might be found. Any transplanted patients are included in all analyses.

Over time, the percentage of patients receiving cranial irradiation decreased substantially with 65%, 35%, and 15% of patients receiving 18 Gy pre-symptomatic whole brain irradiation therapy in the 2nd month of therapy on the CCG-100 series (1983–1988), CCG-1800 series (1989–1995), and CCG-1900 series (1996–2002), respectively.

Table 2 summarizes the data on induction failures, induction deaths, relapses, secondary malignant neoplasm and remission deaths for the three series. The data are presented separately for B-precursor SR and HR, infant, and T-cell ALL. Induction failure rates for the B-precursor SR patients ranged from 0% to 0.4% across the three series and between 0.9% and 1.3% for the HR patients. Induction death rates fell from 1.1% to 0.2% for SR patients; and from 2.5% to 1.4% for the HR patients. Induction death rates for T-cell ALL fell from 2.2% to 1.3% across series. Induction failure rates for infants dropped from 3.1% to 0.9% over time. However the induction death rates increased significantly (3.1%, 1.5%, and 13.0%, respectively) in the last time period.

Relapses are broken down by site, namely, isolated marrow, isolated CNS, and combined or other sites. Isolated marrow relapse comprised about one-half of all relapses across the three series for B-precursor SR patients. Isolated marrow relapse among B-precursor HR patients comprised a similar proportions in the 100 and 1800 series, namely 72% and 78%, but decreased significantly to 59% in the most recent 1900 series. For infants, the proportion of isolated marrow relapses increased (60% vs 73% vs 83%) while the proportion of CNS relapse fell across series. For T-cells, the proportion of isolated marrow relapses remained the same across series (48% to 55%).

Outcomes for various patient subsets are presented in Tables 3–5. Analyses include estimation of outcomes by lineage and NCI risk classification and by study series. Univariate analyses include a variety of presenting features as detailed. Gender, age, WBC, and early marrow response maintained prognostic significance over all three time periods. The prognostic significance of CNS disease at diagnosis increased over the three time intervals as outcomes did not improve for this challenging subset while impropving substantially for patients without CNS disease at diagnosis. Ethnicity lost significance. At 10-years, EFS improved from 51% for black patients diagnosed between 1983 and 1988 (100 series) to 67% for patients diagnosed between 1996 and 2002 (1900 series), while EFS for white patients improved from 63% to 73%. The 5-year EFS for t(1;19), t(4;11), and t(9;22) also improved from 69%, 24%, and 30%, respectively, for the 1800 series to 78%, 44% and 37%, respectively, for the 1900 series. Hypodiploid (<45 chromosomes) and hyperdiploid (> 50 chromosomes) patients went from 35% and 80% to 54% and 83%, respectively, over the same time periods.

As the mix of infants and higher and lower risk patients differed over time, Figures 1–3 display EFS by study series for SR and HR B-precursor, T-cell, and infants, respectively, in order to facilitate cross series comparisons. The EFS and OS improved significantly overtime for SR B-precursor patients ($p<0.0001$ and $p=0.0001$, respectively) and for HR B-precursor patients. For HR T cell patients, 5-year EFS was 58% and 73% in 1983–1988 and 1996–2002 (Tables 3 and 5). For SR T cell patients, 5-year EFS was 68% and 73% in 1983–1988 and 1996–2002 (Tables 3 and 5) with gains to 80% in 1989–1995 (Table 4), which were subsequently lost when SR T-cell patients were assigned to less intensive therapy. The change in outcome for infants was not statistically significant.

For 100 series, 1800 series, and 1900 series patients, the 10-year cumulative incidence rates for death in remission were 2.6±0.3%, 3.0±0.3%, and 3.6±0.7%, respectively (Table 7, figure 4A, B, C). Rates were highest in the infant studies with 5-year remission death rates of 7.0±2.9% and 31.3±5.5% on CCG-1883 and CCG-1953. Ten-year rates were between 1% and 1.5% in the SR studies. On the HR study CCG-1961, the remission death rate was 3.2±0.4% at 5 years and increased to 5.0±1.5% at 10 years. Two of the 4 late deaths are attributed to the late complications of bone marrow transplantation; 1 death was accidental and 1 was unknown.

For 100 series and 1900 series patients, the 10-year cumulative incidence of isolated and combined CNS relapse (Table 7, figure 4A, B, C) decreased from 7.0±0.5% to 4.6±0.3% and 9.5±0.5% to 7.2±0.5%, despite less use of brain irradiation.

For 100 series, 1800 series, and 1900 series patients, the 10-year cumulative incidence of second malignant neoplasm (Table 7, figure 4A, B, C) was 0.7±0.2%, 1.1±0.2%, and 1.0±0.2%, respectively. For SR patients, rates remained between 0.4% and 1.4%.

Discussion

In this report, we review the outcome of 13,298 children with ALL and enrolled in one of sixteen CCG trials between 1983 and 2002. During this period, EFS and OS increased significantly for all groups except infants <1 year of age, who had only a 4-percentage point improvement in 5-year OS. The smallest gains were attained for T-ALL patients with SR features for whom outcomes actually deteriorated between 1989–1995 and 1996–2002, likely due to allocation to less aggressive SR regimens on the CCG-1900 series studies as opposed to treatment on HR regimens in earlier eras. Overall, patients in first remission at 5 years had a consistent 4% risk for an adverse event between 5 and 10 years from diagnosis. This risk was similar for boys and girls.

The results of the randomized questions of these trials have shaped contemporary COG ALL therapy. Vincristine and prednisone pulses, shown to be effective for SR patients as the sole post induction intensification on CCG-161, were the first effective post induction intensification introduced in CCG (5) and remain a part of current COG regimens. Subsequently, every three-week pulses had no advantage over four-weekly pulses on CCG 1891. (26) Recent IBFM data show no advantage for vincristine/dexamethasone pulses in the context of intensive BFM-based therapy (36) but yet more recent EORTC data differ (37) for uncertain reasons. Nonetheless, maintenance vincristine and steroid pulses may now be redundant in the context of more aggressive current BFM-based therapy.

The increased toxicity with combined dexamethasone and anthracycline use in induction is well documented. (38, 39) CCG-105 showed that induction anthracycline added nothing to a three-drug, vincristine, l-asparaginase, and prednisone induction for SR patients who received DI. (9, 10) On CCG-1922, omission of induction anthracycline facilitated near iso-toxic substitution of induction and maintenance dexamethasone for prednisone at a dose ratio of 1 to 6.7 (13) Recent MRC (40) and BFM (41) data support this advantage at ratios of 1 to 6.1 and 1 to 6, with no advantage evident in Japanese (42) and EORTC (43) trials with ratios of 1 to 7.5 and 1 to 10. The CCG-1922 results were not available when CCG 1952 opened and CCG 1952 patients received induction prednisone but subsequent CCG and COG SR ALL trials have used dexamethasone in three-drug induction to good effect. BFM reports excessive dexamethasone morbidity in the context of 4-drug induction that includes daunorubicin. (41).

The Augmented “BFM” regimen, employing longer and stronger post induction intensification, was found superior for HR SER patients on CCG 1882 and has become the mainstay of current COG therapy. (12) The successor trial, CCG 1961, trial found that stronger intensification, derived from the Augmented “BFM” regimen improved outcome for HR RER patients also, but that longer intensification did not. Six months of intensification was as effective as 10 months. (17) Longer intensification also added nothing

for SR patients who received induction dexamethasone on CCG-1991. (18) These findings focus attention on improving the quality of the first six months of post induction therapy.

Administration of the second block of therapy, termed Protocol Ib by the BFM Group and Consolidation by COG, requires approximately two months. Together with similar cyclophosphamide, cytarabine, and 6TG block of DI, this element occupies 3 of the first 7 months of treatment. Despite its long-standing place in treatment, neither its rationale nor its specific contribution is well established. Augmented Consolidation introduced vincristine and asparaginase during the neutropenic periods that follow administration of cyclophosphamide, cytarabine and 6MP. The MRC (UK) reports that the addition of vincristine and asparaginase in Consolidation increases the clearance of minimal residual disease for patients who are still positive at the end of the first month of therapy. (44) COG is now testing Augmented Consolidation for SR B-precursor patients on AALL0331.

The two months of therapy following Ib (BFM) or Consolidation (COG) and preceding Protocol II (BFM) or DI (COG), termed Interim Maintenance (IM) by COG and Consolidation by the BFM Group, have diverged over the years. Earliest BFM and CCG trials employed daily oral 6 MP and weekly oral methotrexate. BFM ALL 86 replaced weekly oral methotrexate with 4 courses of parenteral methotrexate 5 gram/m^2 with leucovorin rescue in protocol M. (45) CCG introduced five courses of vincristine and escalating-dose intravenous methotrexate given every 10–11 days without leucovorin rescue followed by asparaginase during this IM phase on CCG 1882. (12) This Augmented IM phase is now compared to 4 courses of parenteral methotrexate 5 gram/m^2 with leucovorin rescue in the current COG HR B-precursor (AALL0232) and T-cell (AALL0434) trials. Of interest, CCG 5971 found no advantage for every 2 week 5 gram/m^2 methotrexate and leucovorin over weekly oral 20 mg/m^2 methotrexate for patients with lymphoblastic lymphoma. (46) CCG 1991 found better EFS with five courses of vincristine and escalating-dose intravenous methotrexate given every 10–11 days without leucovorin given before and after DI versus of oral methotrexate and 6MP. Thus after 60 years, investigators are still exploring the best ways to administer methotrexate. (19)

CCG 1962 showed that 3 intramuscular (IM) doses of pegylated asparaginase can safely replace 21 IM doses of native asparaginase. The pegylated product provided a superior Day 14 marrow response and lower rates of antibody development. (16) CCG 1961 employed pegylated asparaginase after induction for the augmented arms. (17) POG 9900 changed from 6 doses of native asparaginase 10,000 u/m^2 administered three times a week to one dose of pegylated asparaginase in induction for SR patients. The incidence of end induction minimum residual disease (MRD) positivity (> 10^{-4}) went from 18.9% to 14.3%. (47) Following this, all COG ALL trials now use pegylated rather than native asparaginase, thus sparing children unneeded intramuscular injections.

Several other critical observations emerge from these twenty years of CCG ALL trials. Prevention of relapse is the most effective means to prevent mortality from childhood ALL. Gains were achieved despite no improvement in outcome for patients who relapsed. (48) Freyer et al examined survival after relapse for HR patients on CCG-1961 randomized to more or less effective post induction intensification. (49) Contrary to intuition but in

agreement with other observations excluding intravenous 6MP, post relapse survival was identical for patients relapsing from more and less effective regimens.

As relapse rates decrease over time with improved therapy, remission deaths become larger contributors to overall death rates. The rate of remission deaths is about 1% for SR studies and 3–4% for HR studies, with adolescent patients being at higher risk. Among patients older than 15 years, remission deaths comprise 25% of adverse events.(50) Remission deaths after 5 years may be increasing as more patients receive hematopoietic stem cell transplant in first remission. Bhatia et al comment that about 16% of ALL patients alive and in remission at two years after allogeneic bone marrow will expire in the next 8 years.(51) Transplantation accounts for the increased remission death rate among adolescents and young adults treated according to adult versus pediatric protocols.(52)

Unfortunately, improvements in therapy have been accompanied by increases in toxicity. The most striking has been the increase in avascular necrosis of bone (AVN), which was rarely recognized in patients diagnosed before 1986, but became more common, especially in adolescents and young adults, with the CCG 1800 era trials.(53,54) This complication can lead to significant life-long morbidity with many patients requiring joint replacement surgery during adolescence or early adulthood. AVN has continued to be a problem on subsequent CCG and COG trials. Altered dosing of dexamethasone during DI, i.e., days 1–7 and days 15–21, rather than days 1–21, (55) provide some decrease in the incidence but excessive AVN led to a suspension of the randomization to induction dexamethasone for adolescents on AALL0232.(56) Screening for exceedingly rare anthracycline cardiotoxicity is standard while screening for AVN in older populations with a risk that exceeds 10% has not been adapted. While identification of lesions prior to collapse seems desirable (57), the significance of early MRI findings remains in doubt.(58)

Another lesson learned from these twenty years of trials is the need for adequate sample size to answer critical questions. Statistical power depends on the magnitude of the impact of an intervention and the number of captured events – not patients. As trial planning is based on prior data and outcomes tend to improve over time, baseline event rates are often overestimated. Investigators tend to overestimate the impact of experimental interventions. In the CCG trials, successful experimental regimens provided a 25–40% reduction in risk of failure. If the trials had been designed to detect a 50% or greater reduction in risk of failure, effective interventions, such as dexamethasone for SR ALL, or augmented BFM for HR ALL, may have been missed. Marginal sample size limits opportunity for exploration of potential interactions and generation of novel hypotheses that will support future trials. Sample size estimates should be based on most recent event rates and moderate treatment impact.

With improved outcomes, a geometrically increasing number of patients must be treated to prevent one event (“number needed to treat”). When EFS went from 40% to 60% on CCG-106, (7) a one-third reduction in failures, only five patients had to be exposed to a novel therapy to benefit one patient. Contemporary COG ALL trials require a much larger number to treat. For example, increasing EFS from 88% to 92%, a one third reduction in failure, requires that 25 patients receive the experimental intervention to benefit one patient.

On CCG 1991, 300 doses of parenteral methotrexate prevented one relapse. (19) Increasing EFS through better primary treatment can obviate the need for salvage treatment of prevented relapses, usually morbid and too often ineffective, and provide a net decrease in the use of medical services. (59)

For the future, better ascertainment of patients at higher and lower risk of relapse is critical, and new therapies must be developed that are targeted at the molecular abnormalities that cause leukemia and/or treatment failure. Several important strategies to accomplish these goals are being explored at this time. Most cooperative treatment groups have incorporated minimal residual disease (MRD) testing to identify patients at higher or lower risk of relapse. Patients with an MRD burden greater than 0.01% at end induction have an increased risk of relapse. However in contemporary COG trials, half of relapses still arise among patients with end-induction MRD < 0.01%. (60) Adding a second MRD time point earlier (60) or later (61) in therapy can help to refine MRD-based risk assessment. Minimal residual disease is prognostic in T-cell as well as B-precursor leukemia. (62) The newer genomic technologies including gene expression profiles (63) and arrays to detect genomic copy number alterations (64) may lead to better insight into the molecular basis of leukemogenesis (65) and identify new potential therapeutic targets like JAK2. (66) The roles of pharmacogenomics (67) and patient/family treatment adherence (68) are under study. In Philadelphia chromosome positive chronic myelogenous leukemia(69) and ALL (70), imatinib has made a major impact on outcome. (70) Understanding the mechanism(s) of imatinib resistance has led to novel, effective treatments. (71) One might reasonably hope that understanding of the mechanism(s) of treatment failure in childhood ALL holds similar promise.

Over the past 40 years, cure of this once incurable disease has become commonplace. With deeper insight into leukemia biology, one may only expect that the next twenty years holds similar or greater promise

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Figure 1A

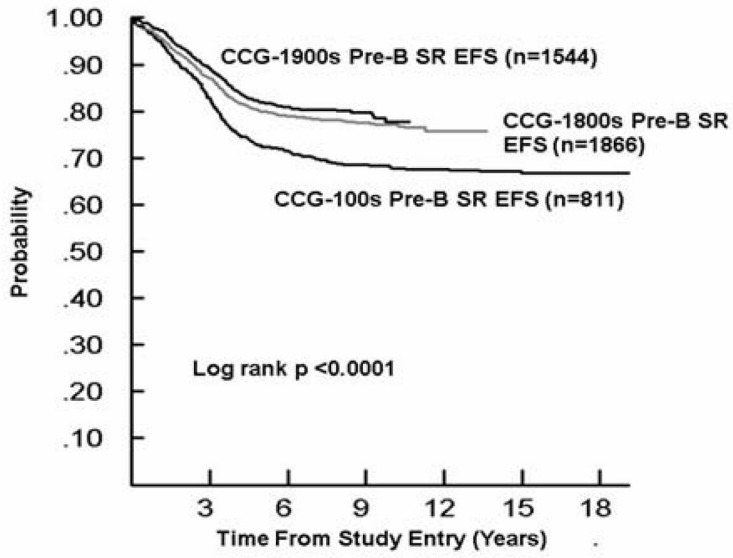


Figure 1B

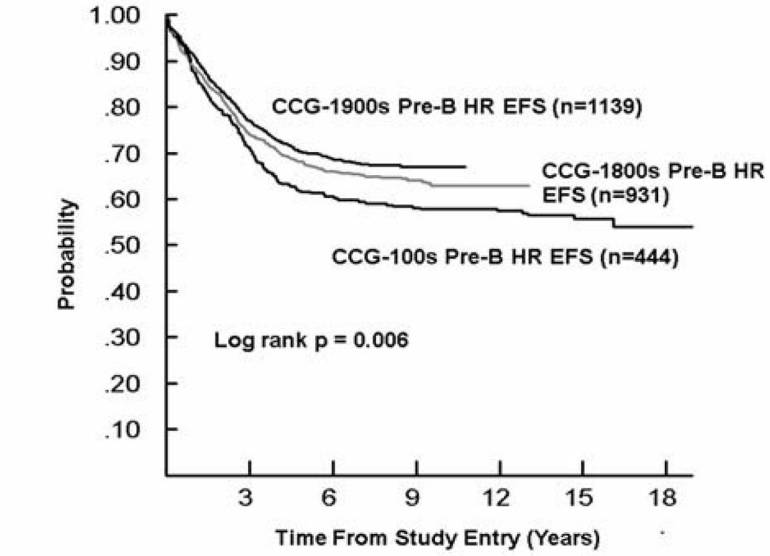


Figure 1. Event-Free Survival for B-precursor ALL by Study Series

a. Standard risk [CCG-100 series (1983–1988), CCG-1800 series (1989–1995), and CCG-1900 series (1996–2002)]; SR, Standard risk; EFS, event-free survival

b. Higher risk [CCG-100 series (1983–1988), CCG-1800 series (1989–1995), and CCG-1900 series (1996–2002)]; HR, high risk; EFS, event free survival

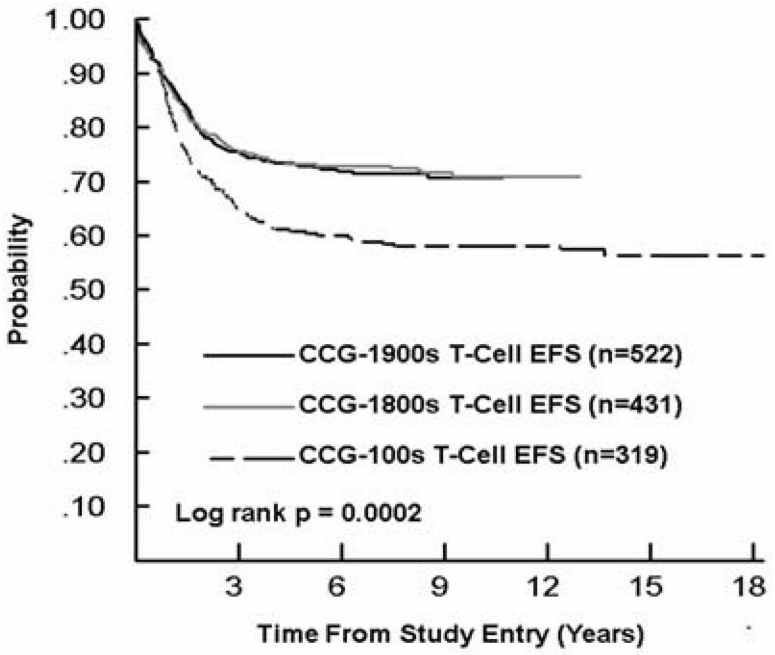


Figure 2.

Event-Free Survival for T-cell ALL by Study Series [CCG-100 series (1983–1988), CCG-1800 series (1989–1995), and CCG-1900 series (1996–2002)] EFS, event-free survival

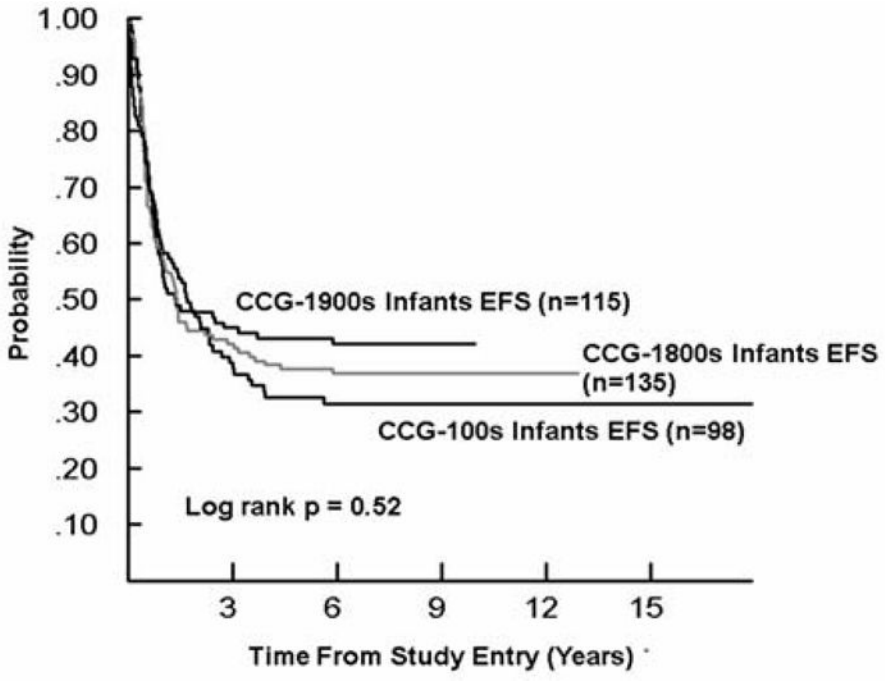
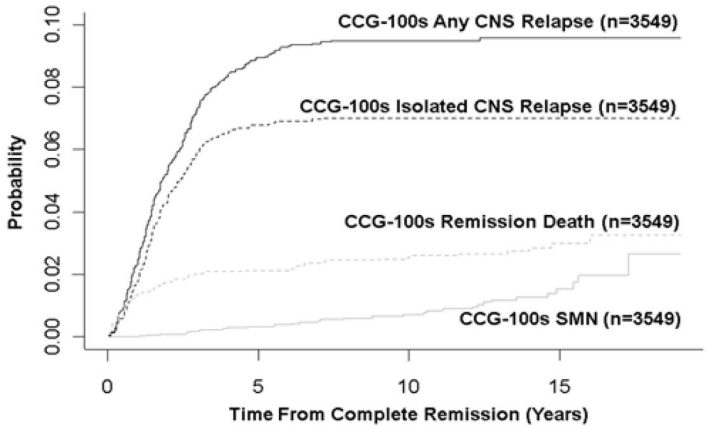


Figure 3.

Event-Free Survival for Infant ALL by Study Series CCG-100 series (1983–1988), CCG-1800 series (1989–1995), and CCG-1900 series (1996–2002)]; EFS, event-free survival

Figure 4A



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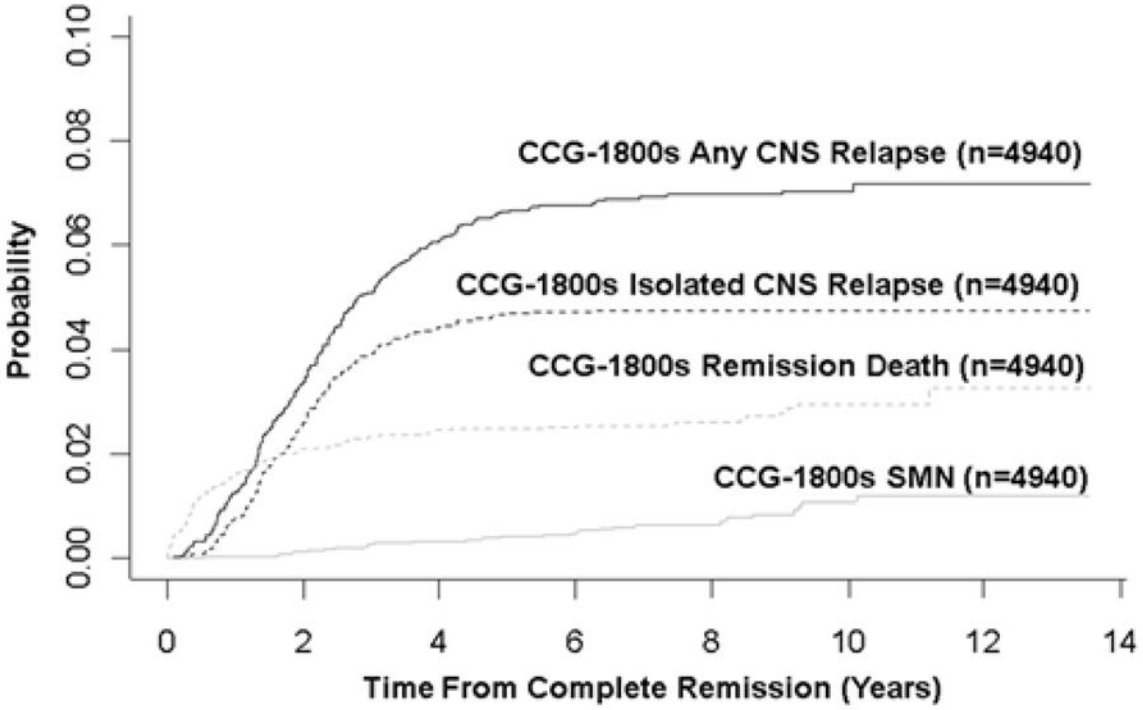

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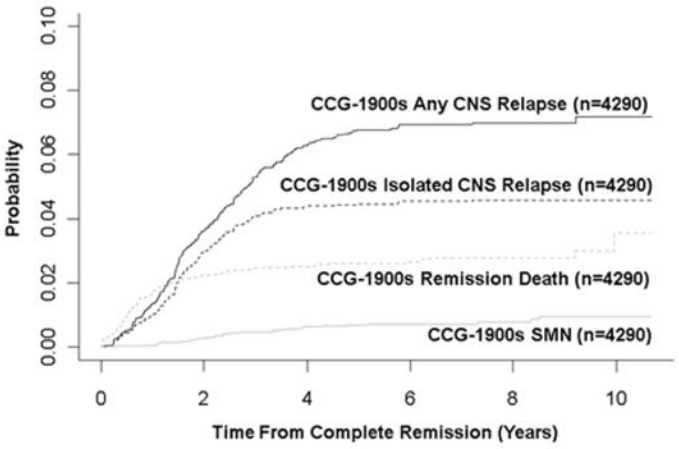

Figure 4. Cumulative Incidence of Remission Death, Isolated Central Nervous System (CNS) Relapse, Any CNS Relapse, and Secondary Malignant Neoplasm (SMN)

a. CCG-100 Series (1983–1988)

b. CCG-1800 Series (1989–1995)

c. CCG-1900 Series (1996–2002)

Table 1

Randomized Questions by study

Study	Population	Question	Result
CCG-105	Intermediate Risk	±Intensive Induction/Consolidation	Intensive induction/consolidation improves EFS but adds adds nothing to Delayed Intensification
		±Delayed Intensification	Better EFS and survival with stronger intensification
		WB XRT vs extended IT Mtx	IT Mtx adequate with intensified systemic therapy
CCG-123	Lymphomatous features	LSA2L2 ± WB XRT BFM NYI	Better EFS and survival with BFM and NY I
CCG-106	Higher risk	“CCG” BFM NYI	Better EFS and survival with BFM and NY I
CCG-139	Standard risk	± Intermediate dose methotrexate (500 mg/m2)	No difference
CCG-1881	Lower risk	±Delayed Intensification	Better EFS with Delayed Intensification
CCG-1891	Intermediate risk (prednisone in induction)	Delayed Intensification x 1 or x 2	Better EFS with double Delayed Intensification
		q3 vs q4 weeks Vcr/Pred pulses	No difference
CCG-1882	Higher risk Rapid early response	WB XRT vs additional IT Mtx	Additional IT Mtx adequate
	Higher risk Slow early response	Longer and stronger post induction intensification	Better EFS and survival with longer and stronger post induction intensification
CCG-1901	Lymphomatous features	NY I vs NY II (extended versus briefer intensification)	NY II less toxic but similarly effective
CCG-1922	Standard risk	Dexamethasone vs prednisone	Better EFS with Dexamethasone
		± IV 6MP	Similar EFS and inferior survival with IV 6MP
CCG-1952	Standard risk	IT triples vs IT Mtx	Fewer CNS relapses but more frequent marrow relapses and inferior survival with IT triples
		Oral 6TG vs Oral 6MP	6TG better, especially in boys with unacceptable liver toxicity
CCG-1961	Higher Risk Rapid early response	Longer versus standard duration intensification	No difference
		Stronger versus standard strength intensification	Better EFS and survival with stronger intensification
	Higher Risk Slow early response	±B43-PAP immunotoxin	Study aborted with loss of drug supply
		Sequential idarubicin/cyclophosphamide versus weekly doxorubicin	No difference
CCG-1962	Standard Risk	Pegylated vs native asparaginase	Pegylated asparaginase similarly effective and less immunogenic

Table 2

Event Summary by series

	CCG 100 series 1983–1988	CCG 1800 series 1989–1995	CCG 1900 series 1996–2002	Total
B-Precursor NCI Standard Risk				
First Event				
No Event	560	1461	1242	3263
Induction Failure	0 (0%)	7 (0.4%)	2 (0.1%)	9 (0.2%)
Induction Death	9 (1.1%)	13 (0.7%)	3 (0.2%)	25 (0.6%)
Relapse	223 (27.5%)	344 (18.4%)	270 (17.5%)	837 (19.8%)
Isolated Marrow	101 (12.4%)	171 (9.2%)	131 (8.5%)	403 (9.5%)
Isolated CNS	64 (7.9%)	103 (5.5%)	65 (4.2%)	232 (5.5%)
Combined and Other	58 (7.2%)	70 (3.7%)	74 (4.8%)	202 (4.8%)
Second Malignancy	3 (0.4%)	8 (0.4%)	8 (0.5%)	19 (0.4%)
Remission Death	16 (2.0%)	33 (1.8%)	19 (1.2%)	68 (1.6%)
Total	811	1866	1544	4221
B-Precursor NCI High Risk				
No Event	257	608	787	1652
Induction Failure	4 (0.9%)	12 (1.3%)	11 (1.0%)	27 (1.1%)
Induction Death	11 (2.5%)	14 (1.5%)	16 (1.4%)	41 (1.6%)
Relapse	152 (34.2%)	244 (26.2%)	277 (24.3%)	673 (26.8%)
Isolated Marrow	110 (24.8%)	191 (20.5%)	163 (14.3%)	464 (18.5%)
Isolated CNS	13 (2.9%)	22 (2.4%)	52 (4.6%)	87 (3.5%)
Combined and Other	29 (6.5%)	31 (3.3%)	62 (5.4%)	122 (4.8%)
Second Malignancy	8 (1.8%)	10 (1.1%)	11 (1.0%)	29 (1.2%)
Remission Death	12 (2.7%)	43 (4.6%)	37 (3.2%)	92 (3.7%)
Total	444	931	1139	2514
Infants				
No Event	31	50	49	130
Induction Failure	3 (3.1%)	2 (1.5%)	1 (0.9%)	6 (1.7%)
Induction Death	3 (3.1%)	2 (1.5%)	15 (13.0%)	20 (5.7%)
Relapse	58 (59.2%)	75 (55.6%)	24 (20.9%)	157 (45.1%)
Isolated Marrow	35 (35.7%)	55 (40.7%)	20 (17.4%)	110 (31.6%)
Isolated CNS	8 (8.2%)	4 (3.0%)	0 (0%)	12 (3.4%)
Combined and Other	15 (15.3%)	16 (11.9%)	4 (3.5%)	35 (10.1%)
Second Malignancy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Remission Death	3 (3.1%)	6 (4.4%)	26 (22.6%)	35 (10.0%)
Total	98	135	115	348
T-Cell				
No Event	187	312	376	875

	CCG 100 series 1983–1988	CCG 1800 series 1989–1995	CCG 1900 series 1996–2002	Total
Induction Failure	5 (1.6%)	9 (2.1%)	5 (1.0%)	19 (1.5%)
Induction Death	7 (2.2%)	7 (1.6%)	7 (1.3%)	21 (1.6%)
Relapse	109 (34.2%)	90 (20.9%)	114 (21.8%)	313 (24.6%)
Isolated Marrow	60 (18.8%)	47 (10.9%)	55 (10.5%)	162 (12.7%)
Isolated CNS	21 (6.6%)	15 (3.5%)	32 (6.1%)	68 (5.4%)
Combined and Other	28 (8.8%)	28 (6.5%)	27 (5.2%)	83 (6.5%)
Second Malignancy	2 (0.6%)	1 (0.2%)	6 (1.1%)	9 (0.7%)
Remission Death	9 (2.8%)	12 (2.8%)	14 (2.7%)	35 (2.8%)
Total	319	431	522	1272

Table 3

CCG-100 series 1983–1988

	# of patients	Event-free survival ± standard error			p-value	Overall survival ± standard error			p-value
		5-year (%)	10-year (%)	15-year (%)		5-year (%)	10-year (%)	15-year (%)	
All patients	3713	65.5 ± 0.8	62.0 ± 0.9	60.6 ± 1.6		78.7 ± 0.7	73.3 ± 0.9	71.31.4	
Infants	98	32.6 ± 4.9	31.5 ± 5.4	31.5 ± 8.3	<0.0001	42.8 ± 5.1	38.2 ± 5.5	38.2 ± 8.7	<0.0001
NCI Higher Risk	1390	58.3 ± 1.4	54.9 ± 1.6	52.9 ± 3.0		68.0 ± 1.3	62.1 ± 1.6	61.5 ± 2.8	
NCI Standard Risk	2225	71.5 ± 1.0	67.8 ± 1.2	66.5 ± 1.9		86.8 ± 0.8	81.8 ± 0.9	79.0 ± 1.6	
B-Lineage	1280	67.9 ± 1.4	63.8 ± 1.6	62.3 ± 2.6	0.003*	81.4 ± 1.1	76.2 ± 1.4	74.4 ± 2.3	<0.0001*
Infants	25	36.0 ± 10.2	36.0 ± 12.9	36.0 ± 16.6	<0.0001	43.6 ± 10.4	43.6 ± 12.4	43.6 ± 18.9	<0.0001
NCI Higher Risk	444	61.6 ± 2.4	57.8 ± 2.8	55.8 ± 4.7		72.3 ± 2.2	65.9 ± 2.7	65.5 ± 4.5	
NCI Standard Risk	811	72.3 ± 1.7	68.0 ± 1.9	66.7 ± 3.1		87.7 ± 1.2	82.9 ± 1.5	80.3 ± 2.6	
T-Lineage	319	60.4 ± 2.9	58.1 ± 3.5	56.3 ± 7.2		69.5 ± 2.8	64.7 ± 3.3	63.5 ± 6.6	
Infants	5	20.0 ± 17.9	20.0 ± 17.9	20.0 ± 17.9	0.004	20.0 ± 17.9	20.0 ± 17.9	20.0 ± 17.9	0.004
NCI Higher Risk	214	58.0 ± 3.7	55.6 ± 4.5	52.7 ± 8.3		65.5 ± 3.5	61.9 ± 4.4	61.9 ± 7.8	
NCI Standard Risk	100	67.6 ± 4.9	65.3 ± 5.4	65.3 ± 13.6		79.7 ± 4.3	72.6 ± 5.0	69.7 ± 12.1	
Gender									
Male	2194	63.0 ± 1.1	58.8 ± 1.2	57.1 ± 2.2	<0.0001	76.9 ± 0.9	71.7 ± 1.1	69.4 ± 1.9	0.002
Female	1519	69.2 ± 1.2	66.6 ± 1.4	65.5 ± 2.3		81.2 ± 1.1	75.6 ± 1.3	74.1 ± 2.1	
Age									
1–9 Years	2788	69.5 ± 0.9	65.9 ± 1.0	64.5 ± 1.7		83.5 ± 0.7	78.6 ± 0.9	76.3 ± 1.5	
≥ 10 Years	827	56.1 ± 1.8	52.3 ± 2.2	50.4 ± 4.1		66.6 ± 1.7	59.6 ± 2.1	58.4 ± 4.0	
Ethnicity									
White	2872	66.6 ± 0.9	63.1 ± 1.0	61.6 ± 1.7	0.0006	79.7 ± 0.8	74.0 ± 0.9	72.1 ± 1.5	0.009
Black	212	56.6 ± 3.6	50.8 ± 4.9	46.9 ± 9.9		69.7 ± 3.4	66.7 ± 4.1	64.8 ± 8.2	
Hispanic	382	61.1 ± 2.7	58.7 ± 3.2	58.0 ± 6.2		75.3 ± 2.4	70.3 ± 2.9	66.1 ± 5.6	
Other	181	64.8 ± 3.7	59.9 ± 4.6	59.9 ± 7.7		80.2 ± 3.1	77.1 ± 3.9	74.8 ± 6.3	
WBC									

	# of patients	Event-free survival ± standard error			p-value	Overall survival ± standard error			p-value
		5-year (%)	10-year (%)	15-year (%)		5-year (%)	10-year (%)	15-year (%)	
<10,000/μl	1640	70.5 ± 1.1	66.0 ± 1.4	64.7 ± 2.2	<0.0001	84.8 ± 0.9	79.2 ± 1.2	76.2 ± 1.9	<0.0001
10,000–50,000/μl	1226	65.8 ± 1.4	62.7 ± 1.6	61.1 ± 2.9		80.6 ± 1.2	74.7 ± 1.5	72.9 ± 2.6	
50,000–100,000/μl	358	60.4 ± 2.8	58.7 ± 3.1	58.7 ± 5.5		70.0 ± 2.6	65.3 ± 3.0	65.3 ± 5.2	
>100,000/μl	488	51.6 ± 2.4	49.0 ± 2.7	46.5 ± 4.8		59.3 ± 2.4	55.9 ± 2.7	55.9 ± 4.7	
CNS at Diagnosis									
Yes	88	59.5 ± 5.6	59.5 ± 6.2	54.0 ± 9.5	0.16	69.7 ± 5.3	66.7 ± 5.9	64.4 ± 9.6	0.08
No	3624	65.6 ± 0.8	62.1 ± 1.0	60.7 ± 1.6		78.9 ± 0.7	73.5 ± 0.9	71.5 ± 1.4	
Day 7 Marrow									
M1	136	75.5 ± 3.8	73.6 ± 4.4	72.1 ± 17.0	<0.0001	79.2 ± 3.6	77.6 ± 4.2	77.6 ± 15.0	0.0008
M2	34	50.0 ± 9.1	50.0 ± 10.2	NA		58.8 ± 8.9	55.2 ± 9.9	NA	
M3	55	42.4 ± 7.2	42.4 ± 9.3	NA		51.5 ± 7.2	51.5 ± 9.3	51.5 ± 25.4	
Day 14 Marrow									
M1	1598	69.8 ± 1.2	66.0 ± 1.4	64.7 ± 2.5	<0.0001	83.7 ± 1.0	78.5 ± 1.2	76.5 ± 2.2	<0.0001
M2	131	56.0 ± 4.6	51.1 ± 5.4	51.1 ± 11.3		73.3 ± 4.1	64.7 ± 5.0	62.2 ± 8.8	
M3	63	28.6 ± 5.9	25.2 ± 6.1	22.4 ± 11.4		44.8 ± 6.5	39.4 ± 7.0	36.8 ± 14.6	

* B-lineage vs. T-lineage

Table 4

CCG-1800 series: 1989–1995

	# of patients	Event-free survival ± standard error			p-value	Overall survival ± standard error			p-value
		5-year (%)	10-year (%)	15-year (%)		5-year (%)	10-year (%)	15-year (%)	
All patients	5121	75.2 ± 0.6	72.1 ± 1.3	NA		85.0 ± 0.5	81.1 ± 1.2	NA	
Infants	135	37.6 ± 4.3	36.8 ± 6.5	NA	<0.0001	50.2 ± 4.4	49.4 ± 7.2	NA	<0.0001
NCI Higher Risk	1841	68.5 ± 1.1	65.1 ± 2.6	NA		76.1 ± 1.1	71.4 ± 2.4	NA	
NCI Standard Risk	3145	80.8 ± 0.7	77.8 ± 1.6	NA		91.7 ± 0.5	88.0 ± 1.2	NA	
B-Lineage	2883	74.6 ± 0.8	71.4 ± 1.7	NA		74.6 ± 0.8	71.4 ± 1.7	NA	
Infants	86	38.0 ± 5.6	38.0 ± 8.0	NA	<0.0001	52.1 ± 5.6	50.8 ± 9.2	NA	<0.0001
NCI Higher Risk	931	67.3 ± 1.6	63.0 ± 3.6	NA		76.0 ± 1.5	69.9 ± 3.4	NA	
NCI Standard Risk	1866	80.0 ± 1.0	77.1 ± 1.9	NA		91.3 ± 0.7	87.1 ± 1.5	NA	
T-Lineage	431	73.2 ± 2.2	71.0 ± 4.6	NA		73.2 ± 2.2	71.0 ± 4.6	NA	
Infants	2	50.0 ± 35.4	NA	NA	0.089	50.0 ± 35.4	NA	NA	0.04
NCI Higher Risk	300	70.3 ± 2.8	68.3 ± 5.6	NA		75.9 ± 2.6	73.9 ± 5.3	NA	
NCI Standard Risk	129	80.2 ± 3.7	77.8 ± 7.6	NA		87.4 ± 3.1	84.7 ± 6.3	NA	
Gender									
Male	2817	74.2 ± 0.9	71.2 ± 1.9	NA	0.1	84.0 ± 0.7	80.0 ± 1.7	NA	0.03
Female	2304	76.5 ± 0.9	73.4 ± 1.9	NA		86.1 ± 0.8	82.5 ± 1.6	NA	
Age									
1–9 Years	3879	79.1 ± 0.7	76.0 ± 1.5	NA		89.6 ± 0.5	85.8 ± 1.2	NA	
≥ 10 Years	1107	66.3 ± 1.5	62.9 ± 3.4	NA		72.8 ± 1.4	68.3 ± 3.3	NA	
Ethnicity									
White	3834	77.2 ± 0.7	74.4 ± 1.5	NA	<0.0001	86.3 ± 0.6	82.8 ± 1.3	NA	<0.0001
Black	291	65.7 ± 3.1	60.9 ± 9.0	NA		78.0 ± 2.7	71.5 ± 8.0	NA	
Hispanic	691	69.1 ± 1.9	65.0 ± 4.3	NA		80.5 ± 1.7	76.2 ± 3.9	NA	
Other	301	73.1 ± 2.7	69.7 ± 5.5	NA		84.3 ± 2.2	80.6 ± 4.8	NA	
WBC									

	# of patients	Event-free survival ± standard error			p-value	Overall survival ± standard error			p-value
		5-year (%)	10-year (%)	15-year (%)		5-year (%)	10-year (%)	15-year (%)	
<10,000/μl	2530	79.0 ± 0.9	75.8 ± 1.8	NA	<0.0001	89.1 ± 0.7	85.4 ± 1.4	NA	<0.0001
10,000–50,000/μl	1514	76.4 ± 1.1	73.5 ± 2.6	NA		86.2 ± 0.9	82.2 ± 2.2	NA	
50,000–100,000/μl	478	70.4 ± 2.2	67.8 ± 4.6	NA		80.3 ± 1.9	75.9 ± 4.3	NA	
>100,000/μl	599	60.1 ± 2.1	56.9 ± 4.5	NA		68.4 ± 2.0	64.4 ± 4.3	NA	
CNS at Diagnosis									
Yes	168	60.2 ± 3.9	56.0 ± 8.5	NA	<0.0001	66.1 ± 3.8	61.3 ± 8.7	NA	<0.0001
No	4903	75.8 ± 0.6	72.8 ± 1.4	NA		85.7 ± 0.5	81.8 ± 1.2	NA	
Day 7 Marrow									
M1	2075	79.7 ± 0.9	77.2 ± 2.3	NA	<0.0001	87.2 ± 0.8	84.4 ± 2.0	NA	<0.0001
M2	926	73.7 ± 1.5	70.8 ± 3.5	NA		85.1 ± 1.2	80.6 ± 3.0	NA	
M3	1025	65.0 ± 1.6	60.4 ± 3.8	NA		76.0 ± 1.4	69.8 ± 3.5	NA	
Ploidy									
Normal	596	81.4 ± 1.7	79.4 ± 3.5	NA	<0.0001	88.8 ± 1.4	85.4 ± 3.0	NA	<0.0001
Hypo <46C	114	57.7 ± 5.0	54.3 ± 11.1	NA		70.3 ± 4.6	65.4 ± 9.9	NA	
45C	91	63.7 ± 5.4	60.9 ± 11.0	NA	0.003*	76.3 ± 4.8	72.3 ± 10.2	NA	0.004*
<45C	23	34.8 ± 9.9	29.0 ± 24.4	NA		47.1 ± 10.8	37.7 ± 29.7	NA	
Pseudo	536	67.5 ± 2.1	63.9 ± 4.2	NA		76.2 ± 1.9	72.3 ± 3.9	NA	
47–50C	206	65.1 ± 3.4	59.9 ± 7.4	NA		79.4 ± 2.9	69.3 ± 6.7	NA	
>50C	494	80.4 ± 1.9	77.6 ± 3.9	NA		90.3 ± 1.4	87.8 ± 3.0	NA	
Translocations									
Normal	1793	76.7 ± 1.0	73.7 ± 2.2	NA	<0.0001	86.1 ± 0.9	82.2 ± 1.9	NA	<0.0001
t(4;11)	42	23.8 ± 6.9	23.8 ± 12.0	NA		30.8 ± 7.4	30.8 ± 14.8	NA	
t(9;22)	44	29.6 ± 7.5	NA	NA		45.1 ± 8.1	22.4 ± 19.7	NA	
t(1;19)	67	68.6 ± 5.8	65.3 ± 10.7	NA		77.6 ± 5.2	71.3 ± 10.2	NA	

*Comparison between 45C and <45C

Table 5

CCG-1900 series: 1996–2002

	# of patients	Event-free survival ± standard error			p-value	Overall survival ± standard error			p-value
		5-year (%)	10-year (%)	15-year (%)		5-year (%)	10-year (%)	15-year (%)	
All patients	4464	76.0 ± 0.7	72.6 ± 2.9	NA		86.3 ± 0.6	82.1 ± 2.5	NA	
Infants	115	43.2 ± 4.8	NA	NA	<0.0001	46.8 ± 4.9	NA	NA	<0.0001
NCI Higher Risk	2054	71.8 ± 1.1	68.5 ± 4.6	NA		81.0 ± 1.0	75.7 ± 4.3	NA	
NCI Standard Risk	2295	81.4 ± 0.9	77.8 ± 3.7	NA		92.9 ± 0.6	89.3 ± 2.8	NA	
B-Lineage	2764	76.0 ± 0.9	72.3 ± 3.7	NA		86.8 ± 0.7	82.1 ± 3.2	NA	
Infants	81	45.3 ± 5.8	NA	NA	<0.0001	49.7 ± 6.0	NA	NA	<0.0001
NCI Higher Risk	1139	70.1 ± 1.5	67.0 ± 6.6	NA		81.0 ± 1.3	74.2 ± 6.3	NA	
NCI Standard Risk	1544	81.9 ± 1.0	77.8 ± 4.3	NA		92.9 ± 0.7	89.2 ± 3.3	NA	
T-Lineage	522	72.8 ± 2.1	70.7 ± 8.4	NA		80.3 ± 1.9	77.3 ± 8.0	NA	
Infants	1	NA	NA	NA	0.02	NA	NA	NA	0.001
NCI Higher Risk	412	72.9 ± 2.4	71.5 ± 9.3	NA		79.4 ± 2.2	77.0 ± 8.7	NA	
NCI Standard Risk	109	73.1 ± 4.4	69.6 ± 19.2	NA		84.6 ± 3.6	80.0 ± 17.9	NA	
Gender									
Male	2557	73.8 ± 0.9	70.3 ± 3.8	NA	<0.0001	85.6 ± 0.7	80.8 ± 3.3	NA	0.05
Female	1907	78.9 ± 1.0	75.7 ± 4.6	NA		87.1 ± 0.8	84.0 ± 3.9	NA	
Age									
1–9 Years	3061	79.4 ± 0.8	75.8 ± 3.3	NA		90.7 ± 0.6	86.1 ± 2.6	NA	
≥ 10 Years	1288	70.9 ± 1.4	67.6 ± 6.3	NA		79.1 ± 1.3	75.9 ± 5.9	NA	
Ethnicity									
White	2996	76.9 ± 0.8	73.1 ± 3.4	NA	0.10	87.2 ± 0.7	83.2 ± 2.9	NA	0.16
Black	216	70.7 ± 3.3	66.7 ± 12.2	NA		82.9 ± 2.8	74.8 ± 11.3	NA	
Hispanic	945	74.9 ± 1.5	73.4 ± 7.2	NA		84.5 ± 1.3	81.4 ± 6.6	NA	
Other	271	74.4 ± 2.8	70.7 ±13.5	NA		85.2 ± 2.3	81.0 ± 12.5	NA	
WBC									

	# of patients	Event-free survival ± standard error			p-value	Overall survival ± standard error			p-value
		5-year (%)	10-year (%)	15-year (%)		5-year (%)	10-year (%)	15-year (%)	
<10,000/μl	2088	80.6 ± 0.9	78.1 ± 3.9	NA	<0.0001	90.3 ± 0.7	87.2 ± 3.2	NA	<0.0001
10,000–50,000/μl	1212	77.0 ± 1.3	71.9 ± 6.0	NA		88.2 ± 1.0	84.1 ± 4.9	NA	
50,000–100,000/μl	531	70.6 ± 2.1	66.6 ± 9.3	NA		81.4 ± 1.8	74.7 ± 8.6	NA	
>100,000/μl	629	63.6 ± 2.1	60.7 ± 7.8	NA		73.1 ± 2.0	67.0 ± 7.4	NA	
CNS at Diagnosis									
CNS Disease	133	57.1 ± 4.7	51.5 ± 17.9	NA	<0.0001	66.1 ± 4.5	53.3 ± 16.3	NA	<0.0001
CNS-2	345	63.5 ± 2.8	61.9 ± 9.3	NA		77.5 ± 2.4	74.2 ± 8.0	NA	
No CNS Disease	3830	77.8 ± 0.7	74.3 ± 3.2	NA		87.9 ± 0.6	84.1 ± 2.7		
Day 7 Marrow									
M1	2005	81.1 ± 0.9	78.8 ± 4.2	NA	<0.0001	89.1 ± 0.8	85.8 ± 3.5	NA	<0.0001
M2	1169	74.6 ± 1.3	72.0 ± 5.3	NA		86.7 ± 1.1	82.7 ± 4.6	NA	
M3	1186	69.6 ± 1.4	64.1 ± 5.9	NA		81.9 ± 1.2	76.2 ± 5.4		
Ploidy									
Normal	663	73.8 ± 1.8	71.6 ± 8.1	NA	<0.0001	87.6 ± 1.4	83.4 ± 6.8	NA	<0.0001
Hypo <46C	165	59.9 ± 4.0	56.8 ± 26.4	NA		75.3 ± 3.6	67.2 ± 22.2	NA	
45C	145	60.7 ± 4.3	58.0 ± 21.7	NA	0.35*	76.9 ± 3.7	73.0 ± 19.0	NA	0.15*
<45C	20	54.2 ± 12.2	47.4 ± 34.4	NA		63.8 ± 11.6	42.6 ± 32.3	NA	
Pseudo	627	69.4 ± 2.0	67.4 ± 9.9	NA		76.8 ± 1.8	74.6 ± 9.1	NA	
47–50C	229	73.6 ± 3.1	67.3 ± 15.7	NA		84.3 ± 2.6	81.2 ± 14.4	NA	
>50C	505	83.3 ± 1.8	80.2 ± 8.0	NA		94.3 ± 1.1	92.6 ± 5.3	NA	
Translocations									
Normal	2008	76.2 ± 1.0	72.8 ± 4.8	NA	<0.0001	86.9 ± 0.8	83.7 ± 4.0	NA	<0.0001
t(4;11)	51	44.1 ± 7.6	39.4 ± 30.7	NA		47.9 ± 7.6	47.9 ± 34.6	NA	
t(9;22)	63	36.7 ± 6.7	NA	NA		45.5 ± 7.2	NA	NA	
t(1;19)	67	77.6 ± 5.5	70.5 ± 38.3	NA		85.0 ± 4.8	85.0 ± 23.3	NA	

*Comparison between 45C and <45C

Table 6

Comparison of EFS and OS by Series

A. B-precursor Standard Risk							
	CCG-100 series (1983–1988)			**CCG-1800 series (1989–1995)**		**CCG-1900 series (1996–2002)**	
n	**811**			**1866**		**1544**	
	5-year (%)	**10-year (%)**	**15-year (%)**	**5-year (%)**	**10-year (%)**	**5-year (%)**	**10-year (%)**
EFS ± SE	72.3 ± 1.7	68.0 ± 1.9	66.7 ± 3.1	79.9 ± 1.0	77.1 ± 1.9	81.9 ± 1.0	77.8 ± 4.4
OS ± SE	87.7 ± 1.2	82.9 ± 1.5	80.3 ± 2.5	91.3 ± 0.7	87.1 ± 1.5	92.9 ± 0.7	89.2 ± 3.3

B. B-precursor Higher Risk							
	CCG-100 series (1983–1988)			**CCG-1800 series (1989–1995)**		**CCG-1900 series (1996–2002)**	
n	**444**			**931**		**1139**	
	5-year (%)	**10-year (%)**	**15-year (%)**	**5-year (%)**	**10-year (%)**	**5-year (%)**	**10-year (%)**
EFS ± SE	61.6 ± 2.4	57.8 ±2.8	55.8 ± 4.7	67.3 ± 1.6	63.0 ± 3.6	70.1 ± 1.5	67.0 ± 6.6
OS ± SE	72.3 ± 2.2	65.9 ± 27	65.5 ± 4.5	76.0 ± 1.5	69.9 ± 3.4	81.0 ± 1.3	74.2 ± 6.3

C. T-Cell							
	CCG-100 series (1983–1988)			**CCG-1800 series (1989–1995)**		**CCG-1900 series (1996–2002)**	
n	**319**			**431**		**522**	
	5-year (%)	**10-year (%)**	**15-year (%)**	**5-year (%)**	**10-year (%)**	**5-year (%)**	**10-year (%)**
EFS ± SE	60.4 ± 2.9	58.1 ± 3.5	56.3 ± 7.0	73.2 ± 2.3	71.0 ± 4.6	72.8 ± 2.1	70.7 ± 8.6
OS ± SE	69.5 ± 2.8	64.7 ± 3.4	63.5 ± 6.5	79.2 ± 2.1	77.0 ± 4.2	80.3 ± 1.9	77.3 ± 8.0

D. Infants							
	CCG-100 series (1983–1988)			**CCG-1800 series (1989–1995)**		**CCG-1900 series (1996–2002)**	
n	**98**			**135**		**115**	
	5-year (%)	**10-year (%)**	**15-year (%)**	**5-year (%)**	**10-year (%)**	**5-year (%)**	**10-year (%)**
EFS ± SE	32.6 ± 4.9	31.5 ± 5.4	31.5 ± 7.9	37.6 ± 4.3	36.8 ± 6.4	43.2 ± 4.8	NA
OS ± SE	42.8 ± 5.1	38.2 ± 5.5	38.2 ± 8.3	50.2 ± 4.4	49.4 ± 7.0	46.8 ± 4.9	NA

Insufficient follow up for 15-yr rates for the 1800 and 1900 series. EFS, p< 0.0001; OS, p=0.0001

Insufficient follow up for 15-yr rates for the 1800 and 1900 series. EFS, p=0.006; OS, p=0.0004

Insufficient follow up for 15-yr rates for the 1800 and 1900 series. EFS, p=0.0002; OS p<0.0001

Insufficient follow up for 15-yr rates for the 1800 and 1900 series. EFS and OS p=ns

Table 7

Post Induction Event Cumulative incidence rates (± standard error)

	CCG-100 series (1983–1988)			CCG-1800 series (1989–1995)			CCG-1900 series (1996–2002)		
n	**3549**			**4940**			**4290**		
	5-year (%)	**10-year (%)**	**15-year (%)**	**5-year (%)**	**10-year (%)**	**15-year (%)**	**5-year (%)**	**10-year (%)**	**15-year (%)**
Remission deaths	2.1± 0.3	2.6± 0.3	3.0 ± 0.4	2.5± 0.2	3.0±0.3	NA	2.6±0.2	3.6±0.7	NA
Isolated CNS relapse	6.8±0.4	7.0±0.5	7.0 ± 0.5	4.7±0.3	4.8±0.3	NA	4.5±0.3	4.6±0.3	NA
CNS relapse Isolated or Combined	8.9±0.5	9.5±0.5	9.6 ± 0.5	6.6±0.4	7.0±0.4	NA	6.8±0.4	7.2±0.5	NA
Second malignant neoplasm	0.3±0.1	0.7±0.2	1.6±0.3	0.4±0.1	1.1±0.2	NA	0.7±0.1	1.0±0.2	NA

n= patients in remission at end of induction