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Long-term Results Of the Pediatric Oncology Group Studies For Childhood Acute Lymphoblastic Leukemia 1984-2001: A Report From The Children's Oncology Group

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Abstract

From 1984-2001, the Pediatric Oncology Group (POG) conducted 12 acute lymphoblastic leukemia (ALL) studies. 10-year event free survival (EFS) for patients >12 months of age with B-precursor ALL on Acute Leukemia in Children 14, 15, and 16 series were 66.7 ± 1.2%, 68.1 ± 1.4% and 73.2 ± 2.1%, respectively. Intermediate dose methotrexate (ID MTX; 1 g/m^2) improved outcomes for standard risk patients (10-year EFS 77.5 ± 2.7% vs. 66.3 ± 3.1% for oral MTX). Neither MTX intensification (2.5 g/m2) nor addition of cytosine arabinoside/daunomycin/ teniposide improved outcomes for higher risk patients. Intermediate dose mercaptopurine (1 g/m^2) failed to improve outcomes for either group. 10-year EFS for patients with T-cell ALL, POG 8704

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CONFLICT OF INTEREST NW has been on the advisory board for both EUSA and Sanofi-Aventis Pharmaceuticals and received compensation of each meeting attended (one each).

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and 9404, were 49.1 ± 3.1% and 72.2 ± 4.7%, respectively. Intensive asparaginase (10-year EFS 61.8% vs 42.7%) and high dose MTX (5 g/m^2) (10-year EFS 78.0% vs. 65.8%) improved outcomes. There was a non-significant improvement in EFS for infants (10-year EFS 17.7 ± 7.2% to 31.9 ± 8.3%). Prognostic indicators for B-precursor ALL were age and WBC at diagnosis, gender, central nervous system disease, DNA index, and cytogenetic abnormalities. Only gender was prognostic in T-cell ALL. In infants, WBC and MLL translocation were linked to inferior outcome.

Keywords

B-lineage ALL; T-lineage ALL; Infant ALL; Prognostic factors; Outcome

INTRODUCTION

Over the past 50 years, there have been dramatic improvements in the outcome of children with acute lymphoblastic leukemia (ALL): 5 year overall survival is now approaching 90%(1-3). During this period, the Pediatric Oncology Group (POG) focused on risk- adapted therapy attempting to both limit toxicities and to maximize cures. Early studies for patients with lower risk B-precursor ALL focused on antimetabolite- based therapy, avoiding the use of anthracyclines, alkylating agents, and epipodophyllotoxins. Because patients with higher risk B-precursor ALL had an inferior outcome with antimetabolite- based therapy alone, further studies investigated the Goldie-Coldman hypothesis by the alternating use of anti-tumor agents that are relatively non-cross resistant to prevent the emergence of (or to treat) drug resistant leukemic clones.

Leukemic cells from children with T- cell ALL and Infant ALL have different biologic characteristics compared to those of children with B-precursor ALL. Therefore, these patients were treated on lineage and age specific protocols. Children with T- cell ALL were initially treated with rotating chemotherapeutic agents, including anthracyclines, alkylators, and epipodophyllotoxins along with intensification of asparaginase. However, because of a high rate of secondary malignancies, subsequent studies focused on intensification with asparaginase and methotrexate. Infants proved difficult to treat throughout this period with high rates of relapse, despite the use of antimetabolites, anthracyclines, alkylators, and epipodophyllotoxins.

From 1984-2001 the POG conducted seven studies for the treatment of B- precursor ALL, two for T- cell ALL and three for Infant ALL. In this paper we report the long term outcomes of patients enrolled on these studies.

MATERIALS AND METHODS

Patients

Between 1984 and 2001, 7393 patients diagnosed with ALL were enrolled on twelve POG studies. Patients with B-precursor ALL (n=6524) were ≥ 12 months to ≤21.999 years of age. Patients with L3 morphology were treated on other studies. Patients with T -cell ALL (n=705) were also ≥ 12 months to ≤21.999 years of age. Infants with ALL (n=164; POG

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8398/8493/9107) were < 12 months of age. The POG 8398 and 8493 infant ALL protocols included infants with B-precursor (non- L3 morphology) and the occasional infant with T-cell ALL. Infants with T- cell ALL were not eligible for POG 9107. For all studies, patients could not have received prior therapy except for emergent treatment with steroids and/or radiation for severe respiratory distress. Blasts were Sudan black and/or myeloperoxidase negative and non-specific esterase negative. Immunophenotyping, chromosome analysis, and DNA index determination were performed at POG reference laboratories for all patients. On ALinC 16, patients also had reference laboratory flouresence in situ hybridization testing for trisomies 4 and 10 and subsets of patients had molecular screening for TEL-AML1 (ETV6-RUNX1) and/or for MLL rearrangements. Infants on the 8398, 8493, and 9107 protocols had subsequent MLL testing from cryopreserved bone marrow samples. All studies were approved by the institutional review board for each participating center. Informed consent was obtained prior to registration and treatment.

Treatments

B-Precursor ALL—Treatments are summarized in Table 1, and included 3 eras, Acute Leukemia in Children (ALinC) 14 - 16. Each POG study was numbered so that the first two numbers indicated the anticipated start year and the second two numbers indicated the study number within the category. POG 8602 (ALinC 14) included patients with both lower and higher risk disease. Subsequently, patients with lower or higher risk disease were treated on separate POG studies. Four POG studies focused on patients with lower risk disease (POG 9005, 9201, 9405, and 9605) and two POG studies focused on patients with higher risk disease (POG 9006 and 9406).

ALinC 14 (1986-1991): POG 8602 evaluated four different schedules of antimetabolite-based therapy (4-6). Patients with lower risk disease had: age 1 - < 3 or 6 - < 11 years and white blood cell (WBC) < $10 \times 10^3/\mu L$, or age 3 - < 6 years and a WBC < $100 \times 10^3/\mu L$. Patients with higher risk disease had: age 1 - < 3 or 6 - < 11 years and WBC ≥ $10 \times 10^3/\mu L$, age 3 - < 6 years and WBC ≥ $100 \times 10^3/\mu L$, or age ≥ 11 years. Patients with central nervous system disease (CNS3) at diagnosis (blasts on cytospin of the cerebrospinal fluid with WBC ≥ 5 cells/μL), or liver and/or spleen extending below the umbilicus, or with pre-B ALL (cytoplasmic immunoglobulin positive) or with Philadelphia chromosome [t(9;22)] positive blasts were considered higher risk disease, regardless of age and WBC. Patients with lower risk disease were randomized to one of the four post-induction regimens: (A) intermediate dose methotrexate (IDMTX) 1 g/m^2, every 3 weeks × 6; (B) IDMTX every 3 weeks × 6 and L-asparaginase (Asp; Merck) 25,000 IU/ m^2 intramuscular (IM) weekly × 24; (C) IDMTX and cytosine arabinoside (AC) 1 g/m^2, every 3 weeks × 6; or (D) IDMTX/AC every 12 weeks × 6. Patients with higher risk disease by age and WBC or by liver/spleen measurement were randomized to regimens B, C, or D. Patients with pre-B ALL were randomized to regimen B or C. Patients who had t(9;22) or CNS3 were non-randomly assigned to regimen C. All patients received CNS prophylaxis with triple intrathecal therapy (TIT) including methotrexate, cytosine arabinoside, and hydrocortisone. Patients with CNS3 at diagnosis received craniospinal irradiation.

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AlinC 15 (1991-1994): ALinC 15 evaluated three schedules of increased intensity methotrexate/mercaptopurine therapy for patients with lower risk disease (POG 9005)(7). Patients with higher risk disease received increased intensity methotrexate/mercaptopurine with or without the addition of epipodophyllotoxins, anthracyclines, and cytosine arabinoside (POG 9006)(8). Patients were risk classified based on age and WBC in the same manner as the POG 8602. Patients with CNS3, t(9;22), t(1:19) or testicular disease were classified as higher risk disease, regardless of age and WBC. Patients with higher risk disease based on age and WBC, no CNS3 disease, and a DNA index (flow cytometric measurement of the DNA of the leukemic blast compared to a normal cell) of > 1.16 were risk adjusted into the lower risk group and treated on the POG 9005. Patients enrolled on the POG 9005 were randomized into three regimens: (A) IDMTX (1g/m^2) and intravenous intermediate dose mercaptopurine (IDMP) 1 g/m^2 every 2 weeks × 12; (B) oral MTX (30 mg/m^2 every 6 hours × 6) and IDMP every 2 weeks × 12; or (C) IDMTX every 2 weeks × 12. Patients enrolled on POG 9006 were randomized into two regimens: (A) IDMTX/IDMP every 2 weeks × 12 or (B) rotating cycles of IDMTX/IDMP, teniposide (VM26)/AC and prednisone/vincristine/daunomycin/Asp/AC (PVDAsp/AC). Patients with t(9;22), t(1;19), or testicular disease were non-randomly assigned to regimen A. Patients with t(9;22) could proceed to transplant at investigator's choice. POG 9006 was later amended to pilot regimen C, which was identical to regimen B except that the IDMTX was 2.5 g/m^2. All patients received CNS prophylaxis with TIT and patients with CNS3 at diagnosis received craniospinal irradiation.

ALinC 16 (1994-1999): ALinC 16 risk stratified patients into lower risk (POG 9201)(9), standard risk (POG 9405 and 9605)(10-12), and higher risk disease (POG 9406). This series first stratified based on age and WBC by National Cancer Institute (NCI) risk grouping: (1) standard risk - age 1 - 9 and WBC < 50 × 10^3/μL, or (2) high risk – age ≥ 10 years or WBC ≥ 50 × 10^3/μL (13). Patients with NCI standard risk and either (1) uninformative cytogenetics and DNA index > 1.16, or (2) trisomies 4 and 10 were classified as having lower risk disease. Patients with NCI standard risk and (1) uninformative cytogenetics and DNA index ≤ 1.16 (or technically unsatisfactory DNA index), or (2) an abnormal karyotype but lacking trisomies 4 and 10; or NCI high risk and (1) uninformative cytogenetics and DNA index > 1.16, or (2) trisomies 4 and 10 were placed in the standard risk group. Patients with NCI high risk and (1) uninformative cytogenetics and DNA index ≤ 1.16 (or technically unsatisfactory DNA index) or (2) an abnormal karyotype but lacking trisomies 4 and 10; or patients with CNS3, t(1;19), t(4;11), or t(9;22) regardless of NCI risk group were placed in the higher risk group. POG 9201, designed to confirm previous outcomes, was a single regimen study utilizing IDMTX for patients with lower risk disease. POG 9405 randomized standard risk patients to two doses of IDMTX (1 versus 2.5 g/m^2) during intensification and to daily versus twice daily MP during continuation. POG 9405 was closed early due to neurotoxicity and replaced by POG 9605; only results from POG 9605 are reported with the ALinC 16 data. POG 9605 randomized patients in a 2×2 factorial design to IM MTX (regimens A/C) versus divided dose (dd) MTX (regimens B/D) (14, 15) and daily (regimens A/B) versus twice daily (regimens C/D) MP. POG 9406 evaluated rotating cycles of relatively non-cross resistant agents and randomized in a 2×2 factorial design to IDMTX, 1 g/m^2 (regimens A/B) versus 2.5 g/m^2 (regimens C/D) and to VM26/AC

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(regimens A/C) versus high dose AC (3 g/m^2 every 12 hours × 4) (HDAC, regimens B/D). All ALinC 16 patients initially received CNS prophylaxis with TIT. Sixteen percent of patients enrolled on 9406/9605 developed grade 3-4 neurotoxicity (60% consisting of seizures). Subsequently, all patients were switched to intrathecal (IT) MTX alone on 9201/9406/9605. Patients with CNS3 at diagnosis received craniospinal irradiation.

T- cell ALL—POG 8704(16) (1987-1992) randomized patients to +/− Asp (Merck) 25,000 IU/ m^2 IM weekly × 20, beginning on day 99 of therapy. The backbone of therapy consisted of rotating combinations including antimetabolites, alkylating agents, anthracyclines, and epipodophyllotoxins. All patients received TIT for CNS prophylaxis. Patients with initial WBC > 50 × 10^3/μL received cranial irradiation and patients with CNS3 at diagnosis received craniospinal irradiation.

POG 9404(17) (1996-2001) randomized patients in a 2×2 factorial design to +/− high dose MTX (5 g/m^2) × 4 doses and to +/− dexrazoxane prior to doxorubicin infusions (18-21). The backbone consisted of V/doxorubicin(Dox)/P/MP every 3 weeks and Asp weekly × 20. All patients received CNS prophylaxis with IT MTX/AC and cranial irradiation. Patients with CNS2 (blasts on cytospin but WBC < 5 cells/μL) or CNS3 at diagnosis received two additional doses of IT therapy.

Infant ALL—All three infant studies (POG 8398, 8493, and 9107) evaluated post-induction rotating cycles of combination chemotherapy. The POG 9407, which opened in 1996, continued as the Children's Oncology Group Study P9407 in 2001, and is not reported here. POG 8398 cycles included intravenous IVMTX/IVMP, VM26/AC, and D/AC(22, 23). All infants received CNS prophylaxis with TIT; infants with CNS3 received additional doses of IT therapy during induction. POG 8493 cycles included VP16/AC, VP/Cy/AC, and MTX/MP(22, 23). All infants received CNS prophylaxis with TIT; infants with CNS3 received 4 additional doses of IT therapy during induction. POG 9107 cycles included HDAC/D, VP16/AC, IVMTX/IVMP, and VP/Cy/AC. All infants received CNS prophylaxis with TIT; no additional therapy was given to patients with CNS3 disease.

STATISTICAL CONSIDERATIONS

Event-free survival 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 time was defined as time from diagnosis to death or last contact. Event-free survival (EFS) and overall survival (OS) rates were computed by the method of Kaplan-Meier and were compared using the log-rank test(24). Cox proportional hazards regression was used to identify independent prognostic factors for EFS. For patients who achieved complete remission (CR), 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 adjusting for competing events(25). Data sets were frozen as of 1/21/2009 for the analyses.

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RESULTS

The 10 year EFS rate improved significantly across eras for patients with B-precursor ALL enrolled on ALinC14 (1986-1991), ALinC15 (1991-1994), and ALinC16 (1992-1999): 66.7 ± 1.2%, 68.1 ± 1.4%, and 73.2 ± 2.1%, respectively ($p < 0.0001$; Fig 1A). The 10 year OS rates for the three eras were 78.8 ± 1.0%, 82.8 ± 1.1%, and 85.3 ± 1.7%, respectively ($p < 0.0001$; Fig 1B). Similar improvements were seen for patients with T-cell ALL on POG 8704 (1987-1992) and POG 9404 (1996-2001): 10 year EFS 49.1 ± 3.1% versus 72.2 ± 4.7%, respectively ($p < 0.0001$; Fig 2A); 10 year OS 55.3 ± 3.1% versus 78.8 ± 4.4%, respectively ($p < 0.0001$; Fig 2B). EFS rates at 10 years for infants enrolled on POG 8398, 8493, and 9107, were of 17.7± 7.2%, 22.4 ± 5.5%, and 31.9 ± 8.3%, respectively. This difference did not however reach statistical significance. Detailed outcomes are given below.

Protocol Specific Treatment Outcome

B-Precursor ALL

ALinC 14: For the 1933 evaluable patients enrolled on ALinC14 (1986-1991), POG 8602, the 10 year EFS and OS were 66.7 ± 1.2% and 78.8 ± 1.0%, respectively (Fig 1A, 1B). Table 2A gives EFS and OS for ALinc14. Table 2B summarizes the outcomes by randomized regimens on POG 8602. Patients with lower risk disease receiving IDMTX (regimen A) had an EFS of 76.3 ± 3.1% and did not have better outcomes with the addition of Asp or AC. Patients with higher risk disease had an EFS of 58% with both of the IDMTX/AC regimens. Patients with pre-B ALL treated with IDMTX/AC at 3 week intervals (regimen C) had an improved outcome compared to those treated with IDMTX/Asp (regimen B) EFS of 70.3 ± 2.9% versus 63.2 ± 3.6% respectively ($p=0.0246$). Table 2C gives a summary of response and first events overall and by NCI risk group. The NCI standard risk patients had a CR rate of 98.2%, while the higher risk patients had a CR rate of 93.4% on this series. Induction failure and induction death rates for the standard risk patients were 0.52% and 0.81%, respectively. Corresponding rates for the higher risk patients were 4.5% and 1.9%, respectively. Table 2D gives the cumulative incidence rates both overall and by study. The 10 year cumulative incidence rates for isolated CNS and any CNS relapses on ALinC 14 were 4.3 ± 0.5% and 7.7 ± 0.6%, respectively (Fig 1C). Cumulative incidence of secondary malignancies at 10 years was 0.6 ± 0.2%, and the incidence rate for remission deaths was 1.9 ± 0.3%.

ALinC 15: EFS and OS at 10 years for the 1896 patients on ALinC15 (1991-1994), POG 9005/9006, were 68.1 ± 1.4% and 82.8 ± 1.1%, respectively (Fig 1A, 1B). EFS and OS for ALinC15 are summarized in Table 2A. Outcomes by randomized regimens are given in Table 2B. Patients with lower risk disease (POG 9005) had a better outcome with IDMTX/IDMP (regimen A) versus lower dose oral MTX/IDMP (regimen B), with an EFS of 77.5 ± 2.7% versus 66.3 ± 3.1% ($p=0.0014$), respectively. However, the addition of IDMP to IDMTX (regimen A) did not improve outcomes over IDMTX alone (regimen C). Acute neurotoxicity occurred in 7.8% of patients enrolled on the 9005, with 82% of events consisting of seizures. Other events included paresthesias, paresis, ataxia, aphasia, dysarthria, debilitating headaches, severe arachnoiditis, and choreoathetosis(26). The incidence of neurotoxicity was higher on regimens A and C (8.3% and 11.2%, respectively)

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than on regimen B (3.7%), p < 0.001. Magnetic resonance imaging (MRI) or computed tomography (CT) evidence of leukoencephalopathy was more commonly present in symptomatic patients on regimens A and C (75% and 77%, respectively) than on regimen B (15.4%), p< 0.001. Patients with higher risk disease (POG 9006) had an EFS of 57.1 ± 2.1% and a similar outcome whether they received IDMTX/IDMP or rotating agents. Table 2C gives a summary of response and first events overall and by NCI risk group for ALinC15. The NCI standard risk patients had a CR rate of 98.3%, while the higher risk patients had a CR rate of 94.9% on this series. Induction failure and induction death rates for the standard risk patients were 0.52% and 0.52%, respectively. Corresponding rates for the higher risk patients were 3.4% and 1.1%, respectively. The cumulative incidence rates on ALinC 15 for isolated CNS and any CNS relapses were 4.8 ± 0.5% and 8.3 ± 0.6%, respectively (Fig 1D, Table 2D). Cumulative incidence of secondary malignancies at 10 years was 0.8 ± 0.2%, and the incidence rate for remission deaths was 1.4 ± 0.3%. Cumulative incidence rates for secondary malignancies at 10 years were 0.7 ± 0.2% and 1.2 ± 0.5% on POG 9005 and 9006, respectively. Remission death rates on the two studies were 0.8 ± 0.3% and 2.8 ± 0.7%, respectively.

ALinC 16: For the 2637 evaluable patients enrolled on ALinC16 (1992-1999), POG 9201/9406/9605, the EFS and OS at 10 years were 73.2 ± 2.1% and 85.3 ± 1.7%, respectively (Fig 1A, 1B). Table 2A summarizes EFS and OS for ALinC16. Patients with lower risk disease and favorable prognostic indicators (DNA index > 1.16 or trisomies 4 and 10) had an EFS of 85.7 ± 2.7% (Table 2B) with IDMTX based therapy alone (POG 9201). Patients with standard risk disease (NCI standard risk with DNA index ≤ 1.16 or lacking trisomies 4 and 10; or NCI higher risk with DNA index > 1.16 or trisomies 4 and 10) had an EFS of 73.4 ± 1.8% (POG 9605). There was a significant interaction between the two randomizations on that study, resulting in insufficient power to determine the superior regimen. Patients with higher risk disease (POG 9406) had EFS of 63.5 ± 1.7% and did not have improved outcomes with the use of HDAC or higher dose MTX. Table 2C gives a summary of response and first events overall and by NCI risk for ALinC16. The NCI standard risk patients had a CR rate of 99.0%, while the higher risk patients had a CR rate of 97.2% on this series. Induction failure and induction death rates for the standard risk patients were 0.23% and 0.29%, respectively. Corresponding rates for the higher risk patients were 1.5% and 1.0%, respectively. Cumulative 10 year incidence rates on ALinC16 for isolated CNS and any CNS relapses were 3.2 ± 0.3% and 6.1 ± 0.5%, respectively (Fig 1E, Table 2D). Overall incidence of secondary malignancies and remission deaths were 0.8 ± 0.2% and 2.0 ± 0.4%, respectively. Incidence of secondary malignancies at ten years was 0.3 ± 0.2%, 0.7 ± 0.3%, and 1.2 ± 0.4%, respectively on POG 9201, 9605 and 9406. Remission death rates were 0.3 ± 0.2%, 1.0 ± 0.4%, and 4.4 ± 0.9%, respectively on the three studies.

T- cell ALL

POG 8704: For 342 evaluable patients enrolled on POG 8704 (1987-1992), the 10 year EFS and OS were 49.1 ± 3.1% and 55.3 ± 3.1%, respectively (Fig 2A, 2B, Table 3A). Patients had an improved outcome with the addition of weekly asparaginase, with 10 year EFS rates of 61.8 ± 4.3% versus 42.7 ± 4.6% (p=0.0012) (Table 3B). Table 3C gives a summary of response and first events for this study. The CR rate at the end of induction was 95.3%.

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Induction failure and induction death rates were 1.5% and 2.6%, respectively. Overall cumulative incidence rates at 10 years for isolated CNS and any CNS relapses were 3.4 ± 1.0% and 9.8 ± 1.7%, respectively (Fig 2C, Table 3D). Overall rate for secondary malignancies at 10 years was 4.0 ± 1.1%. Secondary malignancy rates at 10 years were 6.3 ± 1.9% and 1.9 ± 1.1% for patients receiving or not receiving weekly asparaginase (p=0.11). There were a total of 14 secondary malignancies (10 acute myeloid leukemia (AML), 1 myelodysplastic syndrome (MDS), 1 Acute Lymphoid Leukemia, 1 angiocentric lymphoma, and 1 primitive neuroectodermal tumor). Overall 10 year remission death rate was 3.1 ± 1.0%.

POG 9404: For 363 evaluable patients enrolled on POG 9404 (1996-2001), the 10 year EFS and OS were 72.2 ± 4.7% and 78.8 ± 4.4%, respectively (Fig 2A, 2B, Table 3A). Patients had an improved outcome with the addition of HDMTX with a 10 year EFS of 78.0 ± 6.0% versus 65.8 ± 7.3% (p=0.029; Table 3B). The addition of dexrazoxane had no impact on EFS. Table 3C gives a summary of response and first events for this study. The CR rate at the end of induction was 91.5%. Induction failure and induction death rates were 7.4% and 0.83%, respectively. The 10 year cumulative incidence rates for isolated CNS and any CNS relapses were 7.0 ± 1.4% and 9.4 ± 1.6%, respectively (Fig 2D, Table 3D). Secondary malignancies developed in 2.8 ± 1.2%, and remission deaths occurred in 1.9 ± 0.8% of patients. There were a total of 8 secondary malignancies (3 AML, 1 MDS, 2 non-Hodgkin lymphoma, 1 right cranial tumor, and 1 medulloblastoma). The 10 year cumulative incidence of secondary malignancies were 1.3 ± 0.9% and 4.2 ± 2.2% on the No Dexrazoxane vs Dexrazoxane regimens (p=0.15). Secondary malignancy rates on the No HDMTX vs HDMTX regimens were 4.1 ± 2.3% and 2.3 ± 1.3% (p=0.81), respectively.

Infant ALL—For the 164 evaluable infants on POG 8398 (1984-1990), POG 8493 (1984-1990), and POG 9107 (1991-1993), the overall 10 year EFS and OS rates were 24.1 ± 4.0% and 33.7 ± 4.4%, respectively (Fig 3A). The CR rates (Table 4B) at the end of induction on the three studies were 93.9%, 89.3%, and 89.4%, respectively. Induction failure and induction death rates on 8398 were 6.1% and 0%. Study 8493 had induction failure and induction death rates of 2.4% and 7.1%, respectively. On study 9107, these rates were 2.1% and 6.4%. The overall cumulative incidence rates for isolated CNS and any CNS relapses were 3.4 ± 1.5% and 14.3 ± 2.9%, respectively (Fig 3B, Table 4C). Although outcomes improved progressively over the three studies (EFS 17.7 ± 7.2%, 22.4 ± 5.5%, 31.9 ± 8.3%; Table 4A) this did not reach statistical significance (p=0.66). There were no secondary malignancies seen on either POG 8398 or 8493. Secondary malignancies developed in 3.3 ± 3.4% of patients enrolled on POG 9107. Overall remission death rate at 10 years was 8.2 ± 2.3%.

Treatment Results According to Presenting Features

Univariate and multivariate Cox regression analyses were conducted by presenting features for B-precursor, T-cell, and Infant ALL. Factors considered include, NCI risk, gender, age at diagnosis, race, WBC at diagnosis, CNS status, DNA index, presence of trisomies 4 and 10, TEL-AML1, t(9;22), t(1;19), and t(4;11) translocations. All data (except for TEL-AML1

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status) were available for most of the patients. TEL-AML1 status was known only for 926 patients on the ALinC16 series of studies for B-precursor ALL.

B-precursor ALL—Univariate analyses are summarized in Table 2A for B-precursor ALL. Multivariate analyses (Table 5) included NCI risk, gender, age, race, WBC, CNS status, DI, presence of translocations t(9;22), t(1;19), t(4;11), and trisomies 4 and 10. A total of 4959 patients were included in the analysis. Since TELAML1 status was missing for most of the patients, it was excluded from the multivariate analyses. Males and patients >10 years of age had worse outcomes (HR: 1.5 and 1.64, respectively). Hispanics and blacks had significantly lower EFS compared to whites (HR: 1.39 and 1.29, respectively). Patients with WBC < $10 \times 10^3/\mu L$ have significantly better outcomes compared to those with higher values; those with WBC>$100 \times 10^3/\mu L$ had the worst outcomes. Having CNS disease, or the t(9;22) translocation was associated with poor outcomes (HR: 1.34 and 3.73, respectively). Patients with DI ≤ 1.16 had worse outcomes compared those with 1.16 < DI <1.60. Presence of trisomies 4 and 10 (HR:0.74) and t(1;19) (HR:0.71) were associated with good prognosis. Presence of t(4;11) did not reach statistical significance (HR: 1.37).

T-cell ALL—Univariate analyses are summarized in Table 3A for T-cell ALL. All 705 patients were part of the multivariate Cox regression analyses which included NCI risk, gender, age, race, WBC, and CNS status as prognostic factors (Table 5). Gender was a significant predictor of EFS (HR: 1.744, p=0.0005); males had worse outcomes. No other factors were predictive in the multivariate model.

Infant ALL—Univariate analyses are summarized in Table 4A for Infant ALL. Multivariate analyses included lineage (B-precursor vs T), gender, race, WBC, CNS status, and presence of t(4;11) translocation in the model (Table 5). A total of 148 patients had complete data and were included in the analysis. Patients with 50<WBC<$100 \times 10^3/\mu L$ (HR: 2.132, p=0.0093) and WBC≥$100 \times 10^3/\mu L$ (HR: 2.45, p=0.0003) had worse outcomes compared to WBC<$50 \times 10^3/\mu L$. Presence of the t(4;11) translocation tended to predict poorer outcomes (HR: 1.53, p=0.056).

DISCUSSION

B- Precursor ALL

ALinC 14—All patients received antimetabolite based therapy which was less effective for patients with higher risk disease. No regimen was superior in either risk group, although it should be noted that patients with higher risk disease were not randomized into regimen A (IDMTX alone). In subgroup analysis, patients with pre-B ALL had an improved outcome with every 3 week IDMTX/AC versus every 3 week IDMTX and weekly asparaginase. Outcomes in the IDMTX/Asp group did not correlate with number of doses of asparaginase received.

ALinC 15—POG 9005 intensified therapy by compression of MTX intensification cycles to every 2 weeks (from every 3 weeks on the 8602). In addition IDMP was added to the courses of either IDMTX or PO MTX during intensification. IDMTX/IDMP was superior to PO MTX/IDMP(7). However, these results showed no improvement over those obtained on

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the POG 8602 with IDMTX every 3 weeks without IDMP. In addition, results with IDMTX alone (regimen C) were similar to results of IDMTX/IVMP (regimen A). These data indicated that IDMP did not add benefit to IDMTX. The incidence of acute neurotoxicity was increased on regimens A and C of this trial that included IDMTX every 2 weeks (8.3% and 11.2%, respectively) compared to PO MTX/IDMP, 3.7% ($p < 0.001$). The addition of IDMP to IDMTX did not increase the incidence of acute neurotoxicity over IDMTX alone(26). Neurotoxicity on the POG 9005 was higher than the 2.6% reported on the POG 8602 where IDMTX was administered every 3 weeks(5). Further analyses of the neurotoxicity (mostly seizures) suggested that this was due to a combination of: a. an increased frequency and cumulative dose of IDMTX, b. an increased methotrexate:leucovorin ratio and c. the timing of leucovorin in relation to the intrathecal treatments . There was no evidence implicating an increased risk of neurotoxicity with the use of TIT.

Early results of POG 9006 suggested an improved outcome for higher risk patients treated with rotating cycles of agents, resulting in early trial closure. However, longer follow-up showed no differences in EFS, although toxicity was increased with the rotating cycles of agents (8). This may indicate that agents chosen to test the Goldie-Coldman hypothesis were either not equally effective or were cross resistant. Additionally, the more intensive every 2 week IDMTX/IDMP regimen, like on the POG 9005, provided no improvement in outcome compared to higher risk patients treated on POG 8602.

ALinC 16—POG 9201, utilizing regimen A of POG 8602 confirmed our earlier favorable results for very low risk patients treated with IDMTX based therapy(9, 27-29). The POG 9405 was closed early due to excessive grade 2-4 neurotoxicity (Common toxicity Criteria 2.0) (19% of patients, n=57). More than half of these events were seizures. Other events included cerebellar and motor deficits, cognitive dysfunction, headaches, and significant fatigue. Neither the efficacy nor toxicity of the two MTX schedules could be fully evaluated (10). POG 9605 replaced this study and returned to the intensification regimen A of POG 8602(14, 15). Excessive neurotoxicity was again seen, and the study was amended to replace TIT with IT MTX. Further analysis of neurotoxicity, however, suggested the cause was more complex (see discussion of ALinC 15 above). There was no evidence implicating an increased risk of neurotoxicity with the use of TIT. Although there were no significant differences in outcomes within the MTX and MP study questions, when reviewed by regimen significant differences were evident, with the IM MTX/twice daily MP and dd MTX/daily MP arms demonstrating improved survivals. This suggested that the manner in which these antimetabolites were given influenced outcomes. However, because this trial was designed as a 2×2 factorial, it was not powered to compare the four arms(11, 12).

Higher risk patients, POG 9406, received rotating cycles of non-cross resistant agents based on the early results of POG 9006. Patients were randomized between two doses of IDMTX based on results suggesting that higher steady state MTX levels would improve outcomes and HDAC/Asp versus VM26/AC in an attempt to improve outcomes without increasing the risk of secondary malignancies associated with epipodophyllotoxins. Neither of these strategies improved outcomes.

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ALinC 14-16—The incidence of isolated CNS relapse in patients enrolled on ALinC 14-16 was 3.2 to 4.8% at 10 years, with prophylactic age adjusted IT therapy for all patients and irradiation for patients with CNS3 disease at diagnosis. Despite more aggressive therapy, the incidence of isolated CNS relapse was increased in higher versus lower risk patients, 5.8 ± 0.5% versus 3.2 ± 0.3%, respectively, emphasizing the more resistant nature of the leukemic clone in higher risk patients and suggesting that either the chemotherapeutic agents or their dosing regimens did not provide adequate CNS penetration. A decrease in isolated CNS relapse rate was seen on the POG 9406 with the use of high dose antimetabolite therapy versus intermediate dose antimetabolite therapy utilized on the POG 9006. Other agents with increased CNS penetrance, such as dexamethasone, were not used in these studies, but may play an important role in higher risk disease. Secondary malignancies remained about 1% across all studies, despite the use of epipodophyllotoxins in higher risk patients. Despite increasing intensity across the ALinC 14-16, the percent of patients who failed initial therapy but achieved long term survival remained constant at approximately 50%. This is similar to findings of the Children's Cancer Group, where survival after relapse was not different between earlier and later trials conducted between 1988 and 2002(30).

T-cell ALL

POG 8704—The backbone of rotating agents for this protocol was chosen based on previous combinations that were shown to be effective against T- cell ALL and non-Hodgkin lymphoma(18, 31-33). The addition of asparaginase improved outcome, consistent with outcomes seen on the Dana-Farber Cancer Institute (DFCI) series, where consolidation included both additional doxorubicin and asparaginase(34, 35). Although the rate of secondary malignancies was increased in patients with T-cell ALL receiving asparaginase, this did not reach statistical significance. However, it should be noted that this was a subgroup analysis, and when all patients enrolled on the POG 8704, T-cell ALL and lymphoblastic lymphoma(16), were included in the analysis the use of asparaginase was associated with a significantly increased rate of secondary malignancies. This is consistent with other studies where epipodophyllotoxins were combined with asparaginase(36). Because epipodophyllotoxins are highly bound to plasma proteins, an asparaginase induced decrease in protein synthesis may result in an increase in the unbound epipodophyllotoxin fraction in the plasma and an increased risk of secondary malignancies(37).

POG 9404—The backbone of POG 9404 was based on the Dana-Farber Cancer Institute (DFCI) 87-01, which lacked epipodophyllotoxins but contained anthracyclines that resulted in late cardiac toxicity. The HDMTX regimens had improved outcomes, due to decreased induction failures and CNS relapse rates, and resulted in early closure of the No HDMTX regimens(17). The addition of dexrazoxane did not have an adverse impact on the 10 year EFS. However, late effects of dexrazoxane on cardiac function are still to be determined. Secondary malignancies occurred in 2.8 ± 1.2% of patients, and were not associated with the use of HDMTX or dexrazoxane.

POG 8704/9404—The incidence of isolated CNS relapse in patients enrolled on POG 8704 and on POG 9404 was 3.4% and 7.0%, respectively, at 10 years. All patients received prophylactic age adjusted IT therapy and all CNS3 and higher risk patients on 8704, as well

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as all patients enrolled on POG 9404, received CNS irradiation. Despite the universal application of CNS irradiation on POG 9404, CNS relapse rates did not decrease on this study. This may be a reflection of the limited use of prophylactic IT therapy on the POG 9404 versus 8704, where patients received fewer doses of IT, 10 versus 17, respectively. Overall secondary malignancies in T-cell ALL (2.8 to 4%) remained higher than that for patients with B-precursor ALL. Only 25% of relapsed T-ALL patients achieved long-term survival, significantly lower than similar patients with B-precursor disease.

Infant ALL

Throughout this period results were poor. Although there is a suggestion of improving outcomes, this did not reach statistical significance. The incidence of isolated CNS relapse in patients on POG 8398/8493/9107 was 3.4 ± 1.5% at 10 years, despite using no CNS irradiation due to the certainly of a poor neurocognitive outcome. There was one secondary malignancy at year 12 among the 148 patients in remission on these studies.

Prognostic Indicators

Prognostic indicators identified on the POG studies are similar to those found by other investigators. Significantly, however, gender remained a prognostic indicator on both the B-precursor and T-cell ALL studies. On each of the POG studies, male and female patients were treated with the same duration of therapy. Gender has also been shown to be a prognostic indicator by others, who have chosen to treat males for a year longer than females(38-41). However, it is unclear whether longer duration of therapy or early intensification of therapy actually improves outcomes for males.

CONCLUSION

Over this series of studies we investigated the use of antimetabolite based and rotating agent therapy for the treatment of ALL. The use of IDMTX (1 g/m^2) every three weeks improved outcomes for patients with B-precursor ALL. However, with the exception of HDMTX for the treatment of T-cell ALL, further intensification strategies were unsuccessful, suggesting that we have maximized our ability to eradicate drug resistant clones with antimetabolite based therapy. Additionally, the use of rotating agents had limited impact on higher risk disease. Although this may indicate that the Goldie-Coldman hypothesis is incorrect, it is also possible that the choice or schedule of the agents was not optimal, as other studies utilizing rotating agents have improved outcomes(39, 42, 43). The POG series has demonstrated that patients with lower risk B-precursor ALL can be successfully treated with antimetabolite based therapy, and future studies will need to balance further improvements in outcome against the toxicities associated with therapy. Patients with higher risk B-precursor ALL require therapy directed at early identification(44-48) and treatment of the resistant clone, and may include agents not explored on this series, such as dexamethasone or alkylators. A key strategy to improving the outcome of very high risk patients will be to identify recurrent genetic lesions present in patient subgroups and develop molecularly targeted therapies directed at these lesions, as has been so effective in Ph+ ALL. Patients with T-cell ALL and infant ALL will require novel agents(49, 50), as there is limited ability to further intensify therapy.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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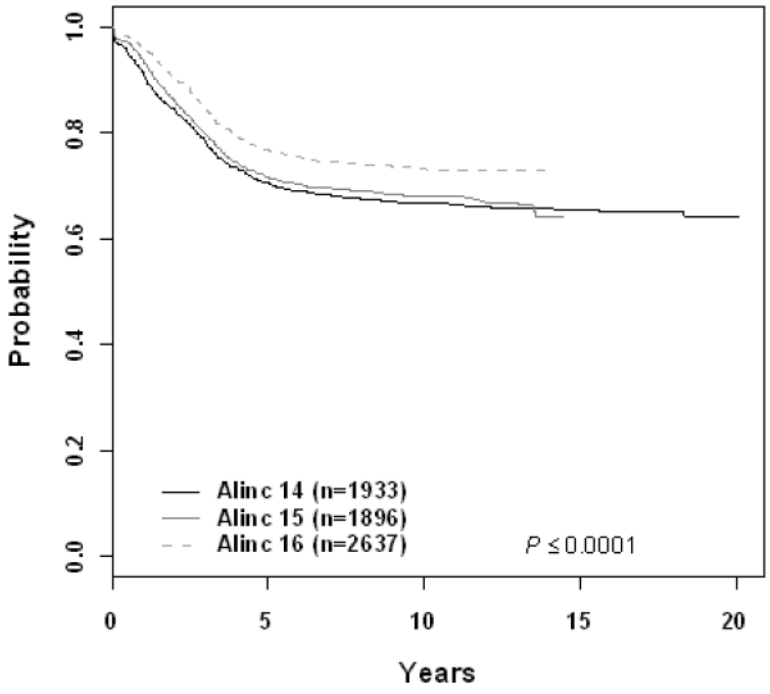

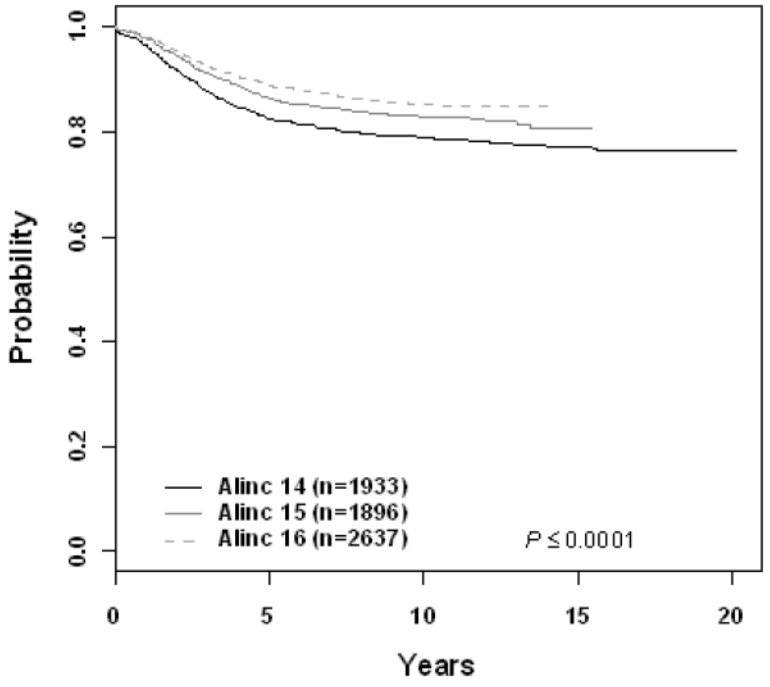

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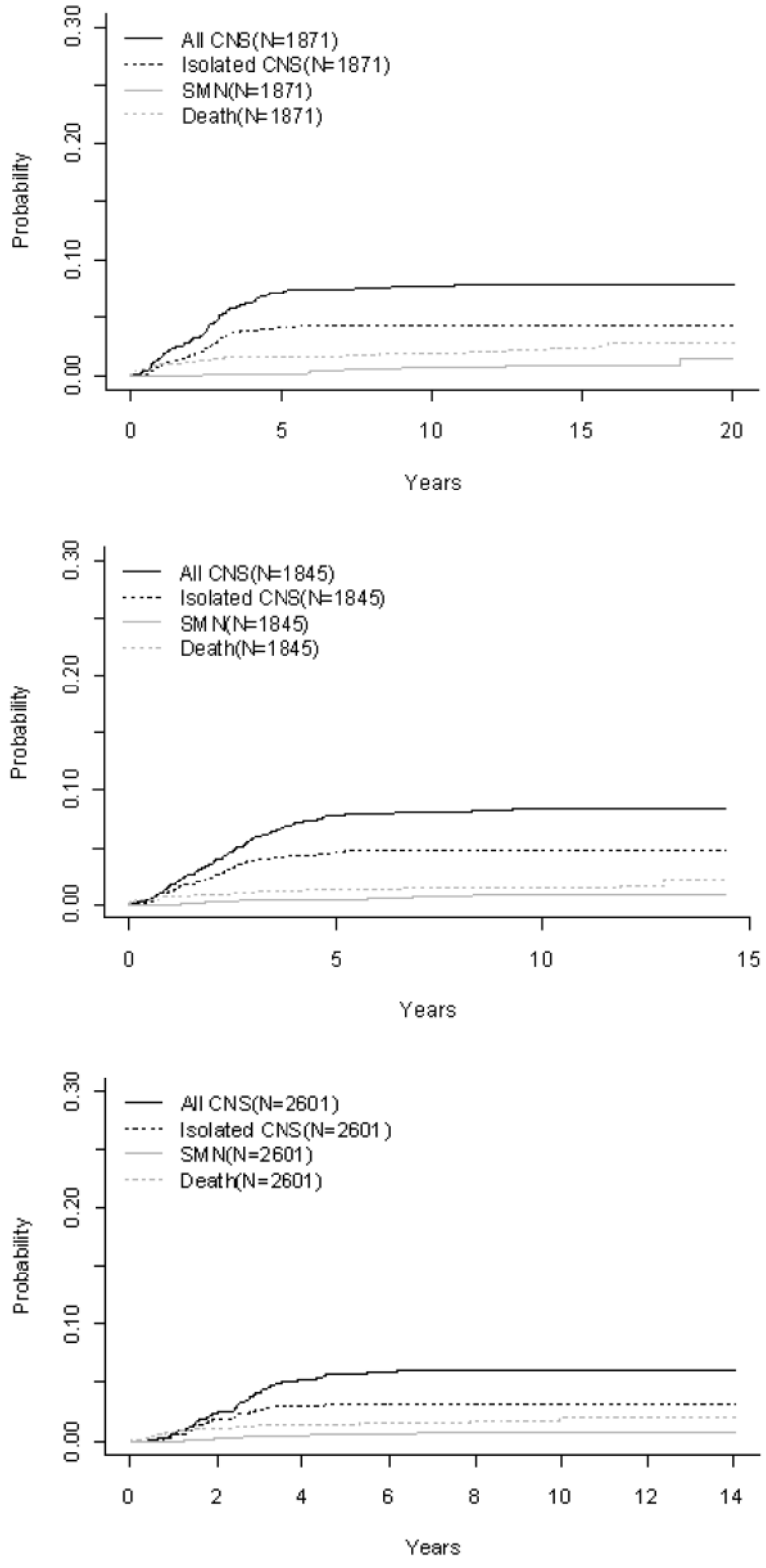

Figure 1.

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B-Precursor ALL (A) Event-Free Survival by Era, (B) Overall Survival by Era, (C) ALinC 14: Cumulative Incidence Rates of all CNS relapse, isolated CNS relapse, SMN, and death, (D) ALinC 15: Cumulative Incidence Rates of all CNS relapse, isolated CNS relapse, SMN, and death, (E) ALinC 16: Cumulative Incidence Rates of all CNS relapse, isolated CNS relapse, SMN, and death

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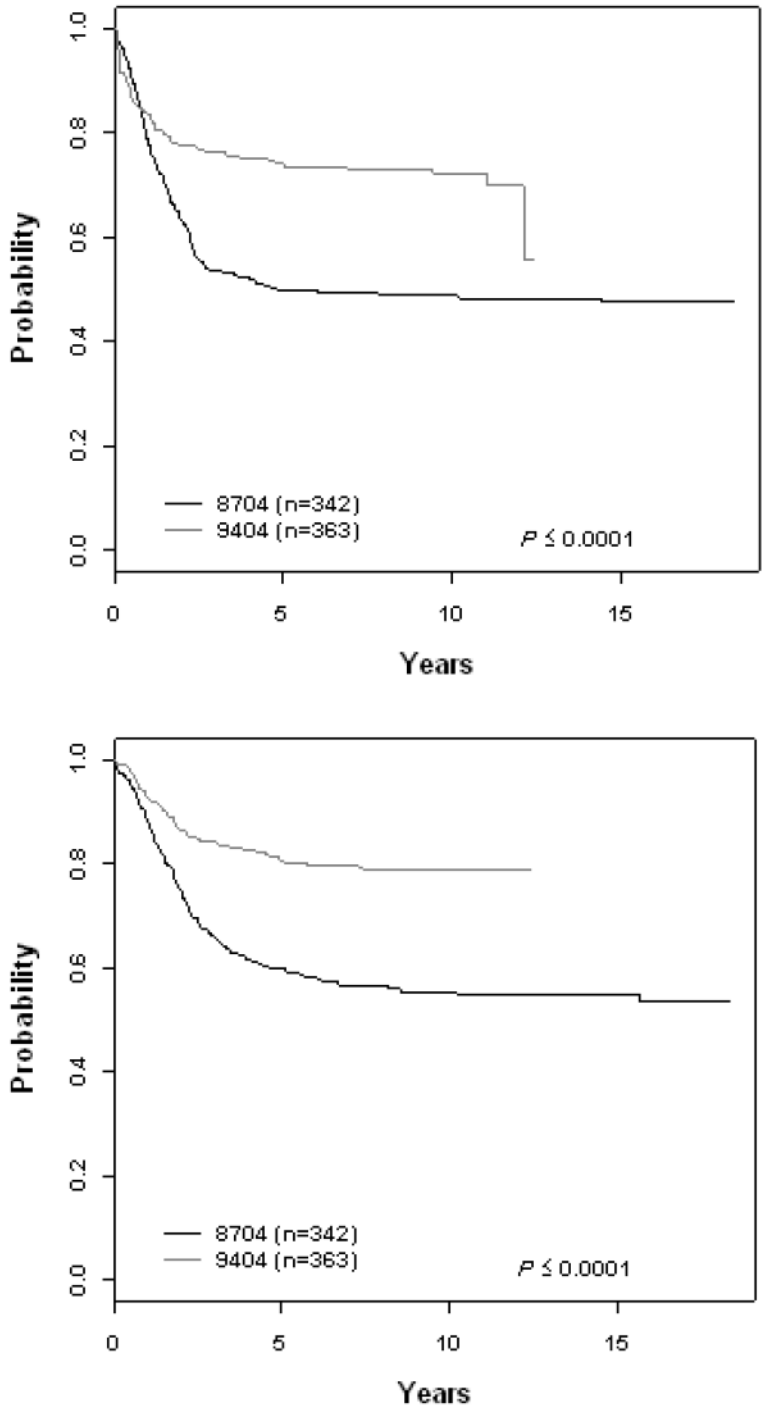

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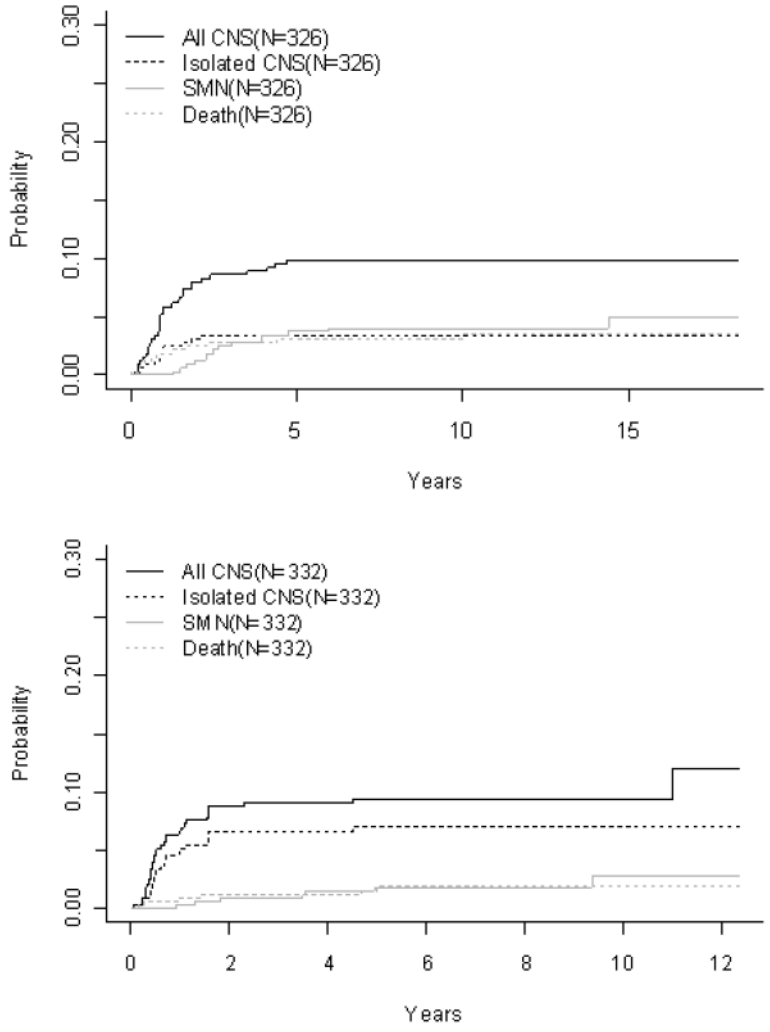

Figure 2.

T-Cell ALL (A) Event-Free Survival by Study, (B) Overall Survival by Study, (C) POG 8704: Cumulative Incidence Rates of all CNS relapse, isolated CNS relapse, SMN, and death, (D) POG 9404: Cumulative Incidence Rates of all CNS relapse, isolated CNS relapse, SMN, and death

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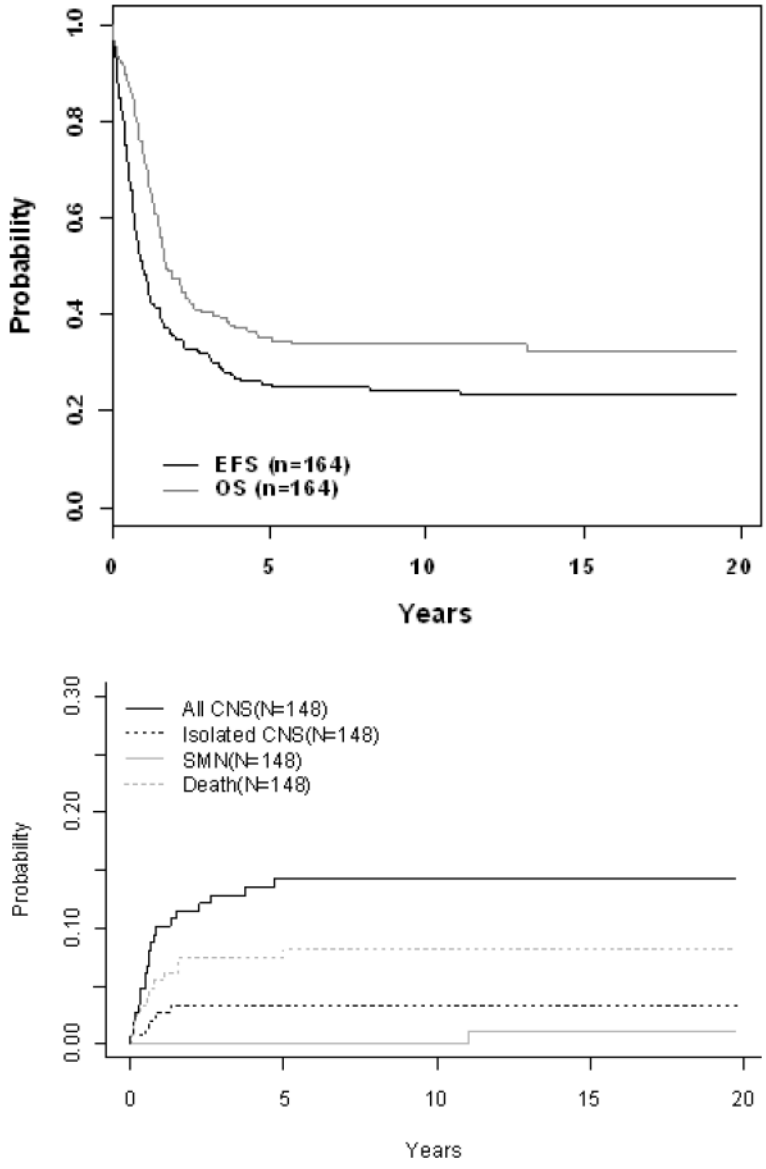

Figure 3.

Infant ALL (A) EFS and Overall Survival, (B) Cumulative Incidence Rates of all CNS relapse, isolated CNS relapse, SMN, and death

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Table 1

Pediatric Oncology Group Treatment Overview

	B-Precursor							T-cell		Infant		
	ALinC 14	**ALinC 15**		**ALinC 16**								
	8602 (1986-1991)	**9005 (1991-1994)**	**9006 (1991-1994)**	**9201 (1992-1999)**	**9405 (1994-1995)**	**9406 (1994-1999)**	**9605 (1996-1999)**	**8704 (1987-1992)**	**9404 (1996-2001)**	**8398 (1984-1990)**	**8493 (1984-1990)**	**9107 (1991-1993)**
Induction	PVAsp	PVAsp	PVDAsp	PVAsp	PVAsp	PVDAsp	PVAsp	PVDoxCy AC/Cy/Asp	PVDox/MTX/MP Randomize (4 groups) ± HDMTX × 4 ± Dexrazoxane	PVDAsp	VP/Cy/AC	VP/Cy/AC
Intensification	Randomize IDMTX q3wk × 6 VP	Randomize IDMTX/IDMP q2wk × 12	Randomize IDMTX (1 g/m^2) + IDMP q2wk × 12	IDMTX q3wk × 6 VP	Randomize IDMTX (1 g/m^2) + IDMP q4wk × 12	Randomize IDMTX (1 g/m^2) + IDMP × 6 VM26/AC × 3 PVDAsp/AC × 3 (30 wk total)	IDMTX q3wk × 6 VP (20 wk total), then Randomize IM MTX qwk × 28 PO MP(qd) VP	AC/VM26 PVDox (8 wk total)	VPDox/MP/Asp (27 wk total)	IVMTX/IVMP × 6 VM26/AC × 3 D/AC × 3 (30 wk total)	VM26/AC (3 wk total) then,	HDAC/D VP16/AC IVMTX/IVMP VP/Cy/AC (52 wk total)
	IDMTX q3wk × 6 + Asp qwk × 24 VP	PO MTX/IDMP q2wk × 12	IDMTX (1 g/m^2) + IDMP × 6 VM26/AC × 3 PVDAsp/AC × 3 (30 wk total)		IDMTX (2.5 g/m^2) + IDMP q4 wk X 12	IDMTX (1 g/m^2) + IDMP × 6 HDAC/Asp × 3 PVDAsp/AC × 3	ddMTX qowk × 14 PO MP(qd) VP				MTX/MP VP/Cy/AC VM26/AC (96 wk total)	
	IDMTX/AC q3wk × 6 VP	IDMTX q2wk × 12	Pilot IDMTX (2.5 g/m^2) + IDMP × 6 VM26/AC × 3 PVDAsp/AC × 3 (30 wk total)			IDMTX (2.5 g/m^2) + IDMP × 6 VM26/AC × 3 PVDAsp/AC × 3	IM MTX qwk × 28 PO MP(BID) VP					
	IDMTX/AC q12wk × 6 VP					IDMTX (2.5 g/m^2) + IDMP × 6 HDAC/Asp × 3 PVDAsp/AC × 3	ddMTX qowk × 14 PO MP(BID) VP					
Continuation	MTX/MP VP q16 wk	MTX/MP	MTX/MP	MTX/MP VP q16 wk	Randomize IM MTX PO MP(BID)	MTX/MP	Continue MP as Randomized IM MTX PO MP VP q16 wk × 4	Randomize AC/Cy PVDox/MP AC/VM26 ± Asp qwk × 20	MTX/MP VP q3 wk	MTX/MP	MTX/MP PV q12 wk	MTX/MP VP16/AC VP/Cy/AC (50 wk total)
					IM MTX PO MP(qd)		IM MTXPO MP(qd) VP q16 wk × 4					

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	B-Precursor							T-cell		Infant		
	ALinC 14	**ALinC 15**		**ALinC 16**								
	8602 (1986-1991)	**9005 (1991-1994)**	**9006 (1991-1994)**	**9201 (1992-1999)**	**9405 (1994-1995)**	**9406 (1994-1999)**	**9605 (1996-1999)**	**8704 (1987-1992)**	**9404 (1996-2001)**	**8398 (1984-1990)**	**8493 (1984-1990)**	**9107 (1991-1993)**
CNS prophylaxis	TIT *ab*	TIT *a*	TIT *ab*	IT MTX *ac*	TIT*a*	IT MTX*abc*	IT MTX*ac*	TIT*a* CXRT*d* or CSXRT *b*	IT MTX/AC*a* CXRT	TIT	TIT	TIT
Duration of Therapy	156 wks from diagnosis	130 wks of CCR	130 wks of CCR	130 wks from diagnosis	130 wks from diagnosis	130 wks of CCR	130 wks from diagnosis	104 wks from diagnosis	104 wks of CCR	130 wks of CCR	156 wks from diagnosis	104 wks of CCR

P-prednisone, V-vincristine, Asp-aspariginase, D-daunomycin, Dox – doxorubicin, Cy-cytoxan, AC-cytosine arabinoside, MTX – methotrexate, MP-6 mercaptopurine, IDMTX-intermediate dose MTX (1 g/m^2 except POG 9006/9405/9406), IDMP-intermediate dose MP (1 g/m^2), HDMTX – High dose MTX (5 g/m^2), VM26 – teniposide, VP16 – etoposide, ddMTX – divided dose MTX, HDAC-high dose cytosine arabinoside

BID – twice daily, TIT intrathecal MTX/AC/hydrocortisone, IT – intrathecal, CCR- continuous complete remission

a age adjusted,

b craniospinal irradiation (CSXRT) for CNS3,

c amended from TIT,

d cranial irradiation (CXRT) for WBC>50,000

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Table 2A

B-precursor ALL: Outcomes by Presenting Features

Factors	No. of patients **	Event-free survival ± SE (%)				Overall survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value	Year 5	Year 10	Year 15	p-value
Era									
ALinC14	1933	70.5 ± 1.1	66.7 ± 1.2	65.4 ± 1.7	< 0.0001	82.3 ± 0.9	78.8 ± 1.0	77.1 ± 1.5	< 0.0001
ALinC15	1896	71.6 ± 1.1	68.1 ± 1.4			86.3 ± 0.8	82.8 ± 1.1	80.5 ± 35.5	
ALinC16	2637	76.9 ± 0.8	73.2 ± 2.1			88.6 ± 0.6	85.3 ± 1.7		
NCI Risk									
Standard	4468	79.2 ± 0.6	75.9 ± 0.9	74.1 ± 1.9	< 0.0001	91.0 ± 0.4	88.3+ 0.7	86.8 ± 1.4	< 0.0001
High	2052	61.3 ± 1.1	56.6 ± 1.7	55.3 ± 3.5		75.7 ± 1.0	70.3 ± 1.5	67.4 ± 3.2	
Gender									
Male	3587	69.5 ± 0.8	65.2 ± 1.2	63.5 ± 2.4	< 0.0001	84.7 ± 0.6	80.9 ± 0.9	79.0 ± 2.0	< 0.0001
Female	2937	78.5 ± 0.8	75.6 ± 1.2	74.0 ± 2.3		87.9 ± 0.6	84.9 ± 0.9	83.1 ± 2.0	
Age at diagnosis									
1-9 yrs	5255	76.9 ± 0.6	73.5 ± 0.9	71.9 ± 1.8	< 0.0001	89.3 ± 0.4	86.5 ± 0.7	85.1 ± 1.4	< 0.0001
≥10 yrs	1269	59.8 ± 1.4	54.7 ± 2.2	52.8 ± 4.9		73.1 ± 1.3	66.3 ± 2.1	62.1 ± 4.5	
Race									
White	4691	75.3 ± 0.6	71.6 ± 0.9	69.7 ± 1.9	< 0.0001	87.7 ± 0.5	84.3 ± 0.7	82.3 ± 1.5	< 0.0001
Black	584	67.1 ± 2.0	63.7 ± 3.0	63.7 ± 6.9		77.1 ± 1.8	73.7 ± 2.7	72.7 ± 6.4	
Hispanic	839	67.2 ± 1.7	63.5 ± 2.9	63.5 ± 7.2		82.2 ± 1.4	76.7 ± 2.5	75.7 ± 7.1	
Other	410	75.7 ± 2.2	71.8 ± 3.3	70.0 ± 5.9		89.4 ± 1.6	88.0 ± 2.4	87.1 ± 4.3	
WBC×10^3/μl									
<10	3561	79.4 ± 0.7	75.7 ± 1.0	73.8 ± 2.1	< 0.0001	90.2 ± 0.5	87.2 ± 0.8	85.3 ± 1.7	< 0.0001
10-50	1947	70.7 ± 1.1	67.2 ± 1.6	65.5 ± 3.2		84.9 ± 0.8	80.6 ± 1.3	79.0 ± 2.8	
50-100	571	65.2 ± 2.0	60.7 ± 3.0	60.1 ± 5.5		80.7 ± 1.7	77.2 ± 2.5	75.2 ± 4.8	
≥100	441	49.7 ± 2.4	46.2 ± 3.7	45.3 ± 9.0		66.4 ± 2.3	62.4 ± 3.3	60.0 ± 7.7	
CNS status									
CNS negative	6322	73.9 ± 0.6	70.3 ± 0.8	68.7 ± 1.7	< 0.0001	86.5 ± 0.4	83.2 ± 0.7	81.4 ± 1.4	< 0.0001
CNS positive	141	56.5 ± 4.2	52.2 ± 6.0	50.7 ± 9.5		69.3 ± 3.9	60.3 ± 5.9	55.1 ± 9.2	
DNA index									
1.16-1.60	1538	83.5 ± 1.0	80.7 ± 1.5	79.4 ± 3.5	< 0.0001	94.7 ± 0.6	92.2 ± 1.0	90.5 ± 2.5	< 0.0001
< 1.16	4383	69.5 ± 0.7	65.7 ± 1.1	63.9 ± 2.2		83.0 ± 0.6	79.3 ± 0.9	77.3 ± 1.9	
Other	41	74.2 ± 7.1	68.7 ± 14.5			87.1 ± 5.4	81.7 ± 12.4		
Trisomy 4 & 10									
Present	1100	86.2 ± 1.1	83.1 ± 1.6	82.4 ± 3.9	< 0.0001	95.9 ± 0.6	94.0 ± 1.0	91.8 ± 2.7	< 0.0001
Absent	4256	70.2 ± 0.7	66.3 ± 1.1	64.5 ± 2.2		83.5 ± 0.6	79.9 ± 0.9	78.0 ± 1.9	
TEL-AML1									
Present	244	86.2 ± 2.3	80.7 ± 8.6		< 0.0001	96.2 ± 1.3	93.8 ± 4.9		< 0.0001

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Factors	No. of patients **	Event-free survival ± SE (%)				Overall survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value	Year 5	Year 10	Year 15	p-value
Absent	682	72.1 ± 1.8	68.8 ± 5.7			84.5 ± 1.4	81.0 ± 4.8		
t(9;22)									
Present	128	24.9 ± 3.9	19.4 ± 4.7	17.0 ± 7.0	< 0.0001	34.8 ± 4.3	32.7 ± 5.5	31.0 ± 9.7	< 0.0001
Absent	5228	74.7 ± 0.6	71.0 ± 0.9	69.4 ± 2.0		87.3 ± 0.5	84.0 ± 0.7	82.1 ± 1.6	
t(1;19)									
Present	259	74.5 ± 2.8	71.4 ± 4.6	71.4 ± 12.1	0.891	83.3 ± 2.4	80.9 ± 3.8	80.9 ± 10.2	0.377
Absent	5097	73.4 ± 0.6	69.7 ± 0.9	68.0 ± 2.0		86.2 ± 0.5	82.9 ± 0.8	80.9 ± 1.6	
t(4;11)									
Present	67	47.8 ± 6.1	46.2 ± 11.3	46.2 ± 24.0	< 0.0001	65.7 ± 5.8	64.1 ± 10.7	64.1 ± 19.2	< 0.0001
Absent	6457	73.8 ± 0.6	70.1 ± 0.8	68.5 ± 1.7		86.4 ± 0.4	82.9 ± 0.7	81.0 ± 1.4	

** The total number of patients is 6524. Of these 58 patients that were on the ALinC17 pilot (run as part of the ALinc16 series) were excluded from the outcome analyses by series (total pts 6466). All 6524 pts are included in the analyses by presenting features. Some presenting features were missing for subsets of patients, and hence totals for each of them do not add up to 6524 pts.

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Table 2B

B-precursor ALL: Randomized Regimen Comparisons

Regimen	No. of patients	Event-free survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value
8602 (lower risk)					
Early Pre-B					
A (Upfront IDM)	228	77.8 ± 2.8	76.3 ± 3.1	74.0 ± 4.4	0.53
B (Upfront IDM & ASP)	295	79.6 ± 2.4	74.6 ± 2.8	71.7 ± 4.1	
A (Upfront IDM)	228	77.8 ± 2.8	76.3 ± 3.1	74.0 ± 4.4	0.25
C (Upfront IDM AC)	399	82.1 ± 1.9	79.2 ± 2.3	78.8 ± 3.2	
C (Upfront IDM AC)	399	82.1 ± 1.9	79.2 ± 2.3	78.8 ± 3.2	0.94
D (IDM AC)	117	84.4 ± 3.4	79.8 ± 4.0	78.3 ± 5.7	
Pre-B					
B (Upfront IDM & ASP)	205	65.2 ± 3.4	63.2 ± 3.6	59.6 ± 5.4	0.0246
C (Upfront IDM AC)	308	74.0 ± 2.5	70.3 ± 2.9	69.9 ± 4.2	
8602 (higher risk)					
C (Upfront IDM ARAC)	354	64.8 ± 2.6	58.8 ± 3.0	58.0 ± 4.3	0.79
D (IDM ARAC)	96	61.3 ± 5.1	57.9 ± 5.6	57.9 ± 7.8	
9005 (lower risk)					
A (ID MTX, ID 6MP)	330	80.2 ± 2.2	77.5 ± 2.7		0.0014
B (PO MTX, ID 6MP)	336	71.4 ± 2.6	66.3 ± 3.1		
A (ID MTX, ID 6MP)	311	78.3 ± 2.4	75.6 ± 3.2		0.30
C (ID MTX)	307	81.2 ± 2.3	78.4 ± 3.1		
9006 (higher risk)					
A (Intensive)	266	60.4 ± 3.0	56.5 ± 4.0		0.24
B (Alternating)	271	63.6 ± 3.0	60.0 ± 3.7		
9201 (lower risk)					
Regimen A	649	88.0 ± 1.3	85.7 ± 2.7		
9605 (Average Risk)					
IMMTX	526	76.9 ± 1.9	72.4 ± 7.8		0.11
ddMTX	537	80.2 ± 1.8	74.5 ± 6.6		
9605 (Average Risk)					
6MP	532	76.8 ± 1.9	71.5 ± 7.1		0.16
dd 6MP	531	80.4 ± 1.8	76.5 ± 7.1		
9605 (Average Risk)					
A (IM MTX/daily MP)	266	71.1 ± 2.8	67.2 ± 3.1		N/A[1]
B (dd MTX/daily MP)	266	82.4 ± 2.4	75.9 ± 4.3		
C (IM MTX/twice daily MP)	260	82.8 ± 2.4	77.8 ± 3		
D (dd MTX/twice daily MP)	271	78 ± 2.6	75.3 ± 2.8		

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Regimen	No. of patients	Event-free survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value
9406 (Higher Risk)					
IDMTX	483	66.9 ± 2.2	61.2 ± 4.9		0.33
Higher dose IDMTX	424	68.7 ± 2.3	66.2 ± 5.4		
9406 (Higher Risk)					
No HDAC	391	70.4 ± 2.4	66.3 ± 5.6		0.41
HDAC	395	73 ± 2.3	67.5 ± 5.7		

[1] powered to answer a 2×2 factorial design, not powered to answer a 4 arm study

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Table 2C

B-precursor ALL: Response and Event Summary by Era

	B-lineage by Series			
	Alinc 14	**Alinc 15**	**Alinc 16**	**Total**
All patients				
First Event				
No Event	1276	1292	1963	4531
Induction Failure	33	26	18	77
Induction Death	22	13	14	49
Relapse	545	522	580	1647
Isolated Marrow	285	274	297	856
Isolated CNS	80	89	82	251
Other	180	159	201	540
Second Malignancy	15	15	19	49
Remission Death	42	28	43	113
Response				
Complete Remission	1871	1845	2601	6317
Induction Failure/Death	49	34	31	114
Other	13	17	5	35
Total	**1933**	**1896**	**2637**	**6466**
NCI Standard Risk				
First Event				
No Event	1003	992	1376	3371
Induction Failure	7	7	4	18
Induction Death	11	7	5	23
Relapse	299	316	325	940
Isolated Marrow	148	166	156	470
Isolated CNS	43	49	47	139
Other	108	101	122	331
Second Malignancy	10	9	10	29
Remission Death	27	12	13	52
Response				
Complete Remission	1333	1320	1722	4375
Induction Failure/Death	18	13	9	40
Other	6	10	2	18
Total	**1357**	**1343**	**1733**	**4433**
NCI High Risk				
First Event				
No Event	273	300	587	1160
Induction Failure	26	19	14	59

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	B-lineage by Series			
	Alinc 14	**Alinc 15**	**Alinc 16**	**Total**
Induction Death	11	6	9	26
Relapse	246	206	255	707
Isolated Marrow	137	108	141	386
Isolated CNS	37	40	35	112
Other	72	58	79	209
Second Malignancy	5	6	9	20
Remission Death	15	16	30	61
Response				
Complete Remission	538	525	879	1942
Induction Failure/Death	31	21	22	74
Other	7	7	3	17
Total	**576**	**553**	**904**	**2033**

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Table 2D

B-precursor ALL: Cumulative Incidence Rates

Patients	Event Type	# of patients	Cumulative Incidence ± SE (%)		
			Year 5	Year 10	Year 15
Alinc 14	Any CNS Relapse	1871	7.2 ± 0.6	7.7 ± 0.6	7.8 ± 0.6
	Isolated CNS Relapse	1871	4.1 ± 0.5	4.3 ± 0.5	4.3 ± 0.5
	Second Malignancy	1871	0.2 ± 0.1	0.6 ± 0.2	0.8 ± 0.2
	Remission Death	1871	1.6 ± 0.3	1.9 ± 0.3	2.3 ± 0.4
Alinc 15	Any CNS Relapse	1845	7.8 ± 0.6	8.3 ± 0.6	
	Isolated CNS Relapse	1845	4.6 ± 0.5	4.8 ± 0.5	
	Second Malignancy	1845	0.4 ± 0.2	0.8 ± 0.2	
	Remission Death	1845	1.3 ± 0.3	1.4 ± 0.3	
Alinc 16	Any CNS Relapse	2601	5.6 ± 0.5	6.1 ± 0.5	
	Isolated CNS Relapse	2601	3.1 ± 0.3	3.2 ± 0.3	
	Second Malignancy	2601	0.6 ± 0.2	0.8 ± 0.2	
	Remission Death	2601	1.5 ± 0.2	2.0 ± 0.4	
POG 8602	Any CNS Relapse	1871	7.2 ± 0.6	7.7 ± 0.6	7.8 ± 0.6
	Isolated CNS Relapse	1871	4.1 ± 0.5	4.3 ± 0.5	4.3 ± 0.5
	Second Malignancy	1871	0.2 ± 0.1	0.6 ± 0.2	0.8 ± 0.2
	Remission Death	1871	1.6 ± 0.3	1.9 ± 0.3	2.3 ± 0.4
POG 9005	Any CNS Relapse	1264	5.8 ± 0.7	6.5 ± 0.7	
	Isolated CNS Relapse	1264	3.2 ± 0.5	3.5 ± 0.5	
	Second Malignancy	1264	0.4 ± 0.2	0.7 ± 0.2	
	Remission Death	1264	0.8 ± 0.3	0.8 ± 0.3	
POG 9006	Any CNS Relapse	581	12.1 ± 1.4	12.3 ± 1.4	
	Isolated CNS Relapse	581	7.6 ± 1.1	7.6 ± 1.1	
	Second Malignancy	581	0.5 ± 0.3	1.2 ± 0.5	
	Remission Death	581	2.2 ± 0.6	2.8 ± 0.7	
POG 9201	Any CNS Relapse	650	3.7 ± 0.8	4.1 ± 0.8	
	Isolated CNS Relapse	650	2.2 ± 0.6	2.2 ± 0.6	
	Second Malignancy	650	0.3 ± 0.2	0.3 ± 0.2	
	Remission Death	650	0.3 ± 0.2	0.3 ± 0.2	
POG 9605	Any CNS Relapse	1068	6.1 ± 0.7	6.8 ± 0.8	
	Isolated CNS Relapse	1068	2.9 ± 0.5	3.2 ± 0.5	
	Second Malignancy	1068	0.7 ± 0.3	0.7 ± 0.3	
	Remission Death	1068	0.7 ± 0.2	1.0 ± 0.4	
POG 9406	Any CNS Relapse	883	6.5 ± 0.8	6.9 ± 0.9	
	Isolated CNS Relapse	883	3.9 ± 0.7	4.0 ± 0.7	
	Second Malignancy	883	0.8 ± 0.3	1.2 ± 0.4	
	Remission Death	883	3.3 ± 0.6	4.4 ± 0.9	

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Table 3A

T-cell ALL: Outcomes by Presenting Features

Factors	No. of patients	Event-free survival ± SE (%)				Overall survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value	Year 5	Year 10	Year 15	p-value
Study									
8704	342	49.7 ± 2.7	49.1 ± 3.1	47.5 ± 5.9	< 0.0001	59.8 ± 2.7	55.3 ± 3.1	54.9 ± 5.0	< 0.0001
9404	363	74.0 ± 2.4	72.2 ± 4.7			80.8 ± 2.2	78.8 ± 4.4		
NCI Risk									
Standard	176	71.5 ± 3.5	69.7 ± 4.8	69.7 ± 10.6	0.0028	80.0 ± 3.1	75.0 ± 4.5	75.0 ± 10.4	0.0050
High	529	59.0 ± 2.2	58.2 ± 3.3	54.4 ± 6.0		67.5 ± 2.1	64.6 ± 3.2	64.1 ± 5.9	
Gender									
Male	530	58.4 ± 2.2	57.5 ± 3.3	53.6 ± 6.5	0.0002	68.4 ± 2.1	64.4 ± 3.1	63.9 ± 6.5	0.0055
Female	175	73.6 ± 3.4	71.8 ± 4.9	71.8 ± 8.8		77.5 ± 3.2	75.7 ± 4.7	75.7 ± 8.4	
Age at diagnosis									
1-9 yrs	412	64.2 ± 2.4	63.1 ± 3.3	59.6 ± 6.2	0.1005	73.8 ± 2.2	70.0 ± 3.1	69.5 ± 6.1	0.0253
≥10 yrs	293	59.3 ± 3.0	58.0 ± 5.2	56.9 ± 10.0		66.1 ± 2.9	63.4 ± 5.0	63.4 ± 9.9	
Race									
White	48	9 62.7 ± 2.2	62.1 ± 3.1	58.8 ± 5.7	0.3594	72.0 ± 2.1	68.9 ± 2.9	68.5 ± 5.6	0.2000
Black	119	58.7 ± 4.8	57.5 ± 8.4	57.5 ± 15.3		63.7 ± 4.7	61.8 ± 8.1	61.8 ± 15.6	
Hispanic	61	67.2 ± 6.2	67.2 ± 11.1	67.2 ± 38.5		73.6 ± 5.9	71.1 ± 10.2	71.1 ± 27.0	
Other	36	58.3 ± 8.2	48.6 ± 20.1			69.4 ± 7.7	55.8 ± 15.2		
WBC×10^3/μl									
<50	299	69.1 ± 2.8	68.0 ± 4.2	67.2 ± 9.1	0.0011	76.4 ± 2.5	72.2 ± 4.0	72.2 ± 8.7	0.004
50-100	126	61.6 ± 4.5	61.6 ± 5.9	53.4 ± 12.2		72.8 ± 4.1	70.2 ± 5.5	70.2 ± 11.6	
≥100	280	54.9 ± 3.0	53.4 ± 4.5	51.5 ± 7.3		63.4 ± 3.0	60.4 ± 4.0	59.5 ± 7.6	
CNS status									
CNS negative	639	61.8 ± 2.0	60.6 ± 2.9	58.2 ± 5.7	0.5555	70.9 ± 1.9	67.2 ± 2.8	66.8 ± 5.6	0.8611
CNS positive	66	65.2 ± 5.9	65.2 ± 8.0	60.1 ± 13.4		68.2 ± 5.8	66.6 ± 8.0	66.6 ± 13.6	

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Table 3B

T-Cell ALL: Randomized Regimen Comparisons

Regimen	No. of patients	Event-free survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value
8704					
No Asp	157	42.7 ± 4.0	42.7 ± 4.6	40.7 ± 7.4	0.0012
Asp	160	63.1 ± 3.8	61.8 ± 4.3	60.2 ± 6.6	
9404 (HDMTX)					
No HDMTX	151	67.5 ± 3.9	65.8 ± 7.3		0.029
HDMTX	148	80.2 ± 3.4	78.0 ± 6.0		
9404 (Dexrazoxane)					
No Dexrazoxane	176	74.4 ± 3.4	73.0 ± 6.4		0.85
Dexrazoxane	187	73.6 ± 3.4	71.3 ± 7.0		

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Table 3C

T-Cell ALL: Response and Event Summary by Study

	T-Cell by Study		
	8704	9404	Total
First Event			
No Event	165	262	428
Induction Failure	5	27	32
Induction Death	9	3	12
Relapse	138	57	195
Isolated Marrow	72	13	85
Isolated CNS	11	23	34
Other	55	21	76
Second Malignancy	14	8	22
Remission Death	11	6	17
Response			
Complete Remission	326	332	658
Induction Failure/Death	14	30	44
Other	2	1	3
Total	**342**	**363**	**705**

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Table 3D

T-Cell ALL: Cumulative Incidence Rates

Study	Event Type	# of patients	Cumulative Incidence ± SE (%)			P-value
			Year 5	Year 10	Year 15	
8704	Any CNS Relapse	326	8.9 ± 1.6	9.8 ± 1.7	9.8 ± 1.7	
	Isolated CNS Relapse	326	3.4 ± 1.0	3.4 ± 1.0	3.4 ± 1.0	
	Second Malignancy	326	3.4 ± 1.0	4 ± 1.1	4.9 ± 1.4	
	Remission Death	326	2.8 ± 0.9	3.1 ± 1.0	3.5 ± 1.0	
9404	Any CNS Relapse	332	9.4 ± 1.6	9.4 ± 1.6		
	Isolated CNS Relapse	332	7.0 ± 1.4	7.0 ± 1.4		
	Second Malignancy	332	1.8 ± 0.7	2.8 ± 1.2		
	Remission Death	332	1.9 ± 0.8	1.9 ± 0.8		
8704						
No ASP	Second Malignancy	156	1.9 ± 1.1	1.9 ± 1.1	3.9 ± 2.2	0.11
ASP		159	5.7 ± 1.8	6.3 ± 1.9	6.3 ± 1.9	
9404 (HDMTX)						
No HDMTX	Second Malignancy	136	2.2 ± 1.3	4.1 ± 2.3		0.81
HDMTX		138	2.3 ± 1.3	2.3 ± 1.3		
9404 (Dexrazoxane)						
No Dexrazoxane	Second Malignancy	159	1.3± 0.9	1.3 ± 0.9		0.15
Dexrazoxane		173	2.3 ± 1.2	4.2 ± 2.2		

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Table 4A

Infant ALL: Outcomes by Presenting Features

Factors	No. of patients	Event-free survival ± SE (%)				Overall survival ± SE (%)			
		Year 5	Year 10	Year 15	p-value	Year 5	Year 10	Year 15	p-value
Study									
8398	33	17.7 ± 7.2	17.7 ± 7.2		0.658	36.4 ± 8.8	36.4 ± 9.2	36.4 ± 16.8	0.558
8493	84	25.0 ± 4.8	22.4 ± 5.5	22.4 ± 7.4		31.6 ± 5.2	30.3 ± 6.0	28 ± 7.9	
9107	47	31.9 ± 7.0	31.9 ± 8.3			40.2 ± 7.3	38.0 ± 9.0		
Cell lineage									
B	159	25.7 ± 3.6	24.3 ± 4.1	23.3 ± 7.7	0.657	35.5 ± 3.9	34.2 ± 4.5	32.7 ± 7.8	0.434
T	5	20.0 ± 17.9	20.0 ± 17.9			20.0 ± 17.9	20.0 ± 17.9		
Gender									
Male	79	26.5 ± 5.1	25.2 ± 5.8	25.2 ± 12.6	0.263	40.5 ± 5.6	37.9 ± 6.2	37.9 ± 10.6	0.151
Female	85	24.7 ± 4.9	23.2 ± 5.4	21.3 ± 9.4		30.0 ± 5.2	30.0 ± 6.3	26.2 ± 11.3	
Race									
White	117	26.4 ± 4.3	24.4 ± 4.7	22.9 ± 9.0	0.532	34.0 ± 4.5	32.1 ± 5.0	30.3 ± 8.4	0.857
Black	20	30.0 ± 10.3	30.0 ± 10.3	30.0 ± 10.3		35.0 ± 10.7	35.0 ± 10.7	35.0 ± 20.0	
Hispanic	20	25.0 ± 9.7	25.0 ± 15.3	25.0 ± 22.0		40.0 ± 11.0	40.0 ± 21.9	40.0 ± 31.0	
Other	7	0 ± 0				42.9 ± 22.9	42.9 ± 22.9		
WBC×10^3/μl									
<50	61	47.3 ± 6.7	43.4 ± 7.9	40.7 ± 15.7	<0.0001	60.5 ± 6.5	56.9 ± 7.6	53.1 ± 12.9	< 0.0001
50-100	29	13.8 ± 6.4	13.8 ± 6.4	13.8 ± 12.8		20.7 ± 7.5	20.7 ± 9.2	20.7 ± 18.4	
≥100	73	12.3 ± 3.9	12.3 ± 4.4	12.3 ± 8.2		19.8 ± 4.8	19.8 ± 5.4	19.8 ± 10.3	
CNS status									
CNS negative	112	27.6 ± 4.4	25.6 ± 4.9	24.1 ± 8.6	0.855	38.9 ± 4.8	37.0 ± 5.5	34.8 ± 8.9	0.409
CNS positive	37	27.0 ± 7.7	27.0 ± 8.7	27.0 ± 23.1		29.7 ± 7.9	29.7 ± 9.4	29.7 ± 24.9	
t(4;11)									
Present	52	15.4 ± 5.4	15.4 ± 5.8	15.4 ± 14.2	0.017	25.0 ± 6.3	22.9 ± 7.1	22.9 ± 14.2	0.024
Absent	112	30.2 ± 4.5	28.2 ± 5.1	26.8 ± 9.4		39.7 ± 4.8	38.8 ± 5.5	36.8 ± 9.3	

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Table 4B

Infant ALL: Response and Event Summary by Study

	Infants by Study			
	8398	8493	9107	Total
First Event				
No Event	6	19	14	39
Induction Failure	2	2	1	5
Induction Death	0	6	3	9
Relapse	23	51	24	98
Isolated Marrow	13	35	17	65
Isolated CNS	0	3	2	5
Other	10	13	5	28
Second Malignancy	0	0	1	1
Remission Death	2	6	4	12
Response				
Complete Remission	31	75	42	148
Induction Failure/Death	2	7	4	13
Other	0	2	1	3
Total	**33**	**84**	**47**	**164**

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Table 4C

Infant ALL: Cumulative Incidence Rates

Study	Event Type	# of patients	Cumulative Incidence ± SE (%)		
			Year 5	Year 10	Year 15
Overall	Any CNS Relapse	148	14.3 ± 2.9	14.3 ± 2.9	14.3 ± 2.9
	Isolated CNS Relapse	148	3.4 ± 1.5	3.4 ± 1.5	3.4 ± 1.5
	Second Malignancy	148	0 ± 0	0 ± 0	1.1 ± 1.1
	Remission Death	148	7.4 ± 2.2	8.2 ± 2.3	8.2 ± 2.3
8398	Any CNS Relapse	31	16.7 ± 7.2		
	Isolated CNS Relapse	31	0 ± 0		
	Second Malignancy	31	0 ± 0		
	Death	31	6.5 ± 4.6		
8493	Any CNS Relapse	75	14.7 ± 4.1	14.7 ± 4.1	14.7 ± 4.1
	Isolated CNS Relapse	75	4.0 ± 2.3	4.0 ± 2.3	4.0 ± 2.3
	Second Malignancy	75	0 ± 0	0 ± 0	0 ± 0
	Death	75	6.7 ± 2.9	8.1 ± 3.2	8.1 ± 3.2
9107	Any CNS Relapse	42	11.9 ± 5.1	11.9 ± 5.1	
	Isolated CNS Relapse	42	4.8 ± 3.3	4.8 ± 3.3	
	Second Malignancy	42	0 ± 0	3.3 ± 3.4	
	Death	42	9.5 ± 4.6	9.5 ± 4.6	

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Table 5

Multivariate Analyses

Patients	N	Factor	p-value	Hazard Ratio
Infant ALL	148	LINEAGE: T vs. B	0.2284	2.162
		GENDER: M vs. F	0.4931	0.868
		RACE: Black vs. White	0.3654	0.759
		RACE: Hispanic vs. White	0.9852	1.006
		RACE: Other vs. White	0.6489	1.229
		WBC: 50-100 vs. <50	0.0093	2.132
		WBC: ≥100 vs. <50	0.0003	2.448
		CNS status: Pos vs. Neg	0.8113	1.062
		MLL: Present vs. Absent	0.0564	1.527
Non-Infant B-precursor ALL	4959	NCI Standard vs. High risk	0.7534	0.960
		GENDER: M vs. F	<.0001	1.498
		AGE: >10 vs. 1-9	<.0001	1.644
		RACE: Black vs. White	0.0026	1.287
		RACE: Hispanic vs. White	<.0001	1.386
		RACE: Other vs. White	0.9544	0.993
		WBC: 10-50 vs. <10	<.0001	1.425
		WBC: 50-100 vs. <10	<.0001	1.630
		WBC: ≥100 vs. <10	<.0001	2.456
		CNS status: Pos vs. Neg	0.0382	1.342
		DI: <=1.16 vs. 1.16-1.60	0.0002	1.415
		DI: Other vs. 1.16-1.60	0.3406	1.413
		t(9;22): Present vs. Absent	<.0001	3.734
		t(1;19): Present vs. Absent	0.0079	0.710
		t(4;11): Present vs. Absent	0.0884	1.367
		TRISOMY4/10: Present vs. Absent	0.0049	0.740
Non-Infant T-cell ALL	705	NCI Standard vs. NCI High	0.6604	0.894
		GENDER: M vs. F	0.0005	1.744
		AGE: >10 vs. 1-9	0.1782	1.226
		RACE: Black vs. White	0.1472	1.264
		RACE: Hispanic vs. White	0.8702	0.962
		RACE: Other vs. White	0.2570	1.327
		WBC: 50-100 vs. <50	0.5622	1.141
		WBC: ≥100 vs. <50	0.0649	1.437
		CNS status: Pos vs. Neg	0.3244	0.809