Published in final edited form as:

Pediatr Blood Cancer. 2013 June ; 60(6): 957–963. doi:10.1002/pbc.24420.

Children's Oncology Group's 2013 Blueprint for Research: Acute Lymphoblastic Leukemia

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Abstract

Approximately 90% of the 2,000 children, adolescents, and young adults enrolled each year in Children's Oncology Group acute lymphoblastic leukemia (ALL) trials will be cured. However, high-risk subsets with significantly inferior survival remain, including infants, newly diagnosed patients with age < 10 years, white blood count > 50,000/ μ l, poor early response or T-cell ALL, and relapsed ALL patients. Effective strategies to improve survival include better risk stratification, optimizing standard chemotherapy and combining targeted therapies with cytotoxic chemotherapy, the latter of which is dependent upon identification of key driver mutations present in ALL.

Keywords

acute lymphoblastic leukemia (ALL); COG ALL trials

INTRODUCTION

The goals of this Blueprint are to summarize current knowledge regarding the biology and treatment of childhood acute lymphoblastic leukemia (ALL), to review the major findings from recent Children's Oncology Group (COG) ALL trials and translational research efforts, and to outline plans for COG ALL clinical trials scheduled to open in the near future. The efforts of groups throughout the world have made childhood ALL a highly curable disease, but a review of the results of non-COG ALL trials is beyond the scope of this report.

STATE OF THE DISEASE—CLINICAL

Overview and Incidence

ALL is the most common pediatric malignancy, comprising 25% of cancers occurring before 15 years of age and 19% among those less than 20 years old [1]. Despite steady improvements in outcome, ALL remains the leading cause of childhood cancer death [2].

Staging/Stratification

Clinical trials have identified a number of features predictive of outcome, including initial age and white blood cell count (WBC), immunophenotype, presence/absence of central nervous system (CNS) or testicular leukemia, presence/absence of specific sentinel genetic lesions (good risk: *ETV6-RUNX1* fusion or hyperdiploidy with favorable chromosome trisomies; poor risk: *MLL*-rearrangements (*MLL*-R), hypodiploidy, intrachromosomal amplification of chromosome 21 (iAMP21), Philadelphia chromosome positive (Ph⁺) ALL), and early treatment response, which is assessed now by most groups via measurement of minimal residual disease (MRD) at specific timepoints early in therapy. The COG has developed a system that integrates these factors, including National Cancer Institute (NCI) risk group [3] (standard risk (SR): age 1–9.99 years and initial WBC <50,000/μl; high risk (HR): age 10+ years and/or initial WBC ≥50,000/μl), for risk stratification and treatment allocation [4–6]. The current risk stratification system (AALL08B1; Table I) builds on that developed for the first generation COG ALL trials (AALL03B1) with key differences being changing the MRD threshold used to define poor response from 0.1% (AALL03B1) to 0.01% (AALL08B1) at end Induction, and incorporating Day 8 peripheral blood MRD measurements while eliminating Day 8/15 bone marrow (BM) aspirates for morphology. Most international groups assess MRD via molecular methods, but the COG has utilized flow-based MRD in clinical trials and has the largest experience with this modality with over 12,000 patients allocated to different treatments based on flow MRD response.

Current Outcome

The 5-year overall survival (OS) for ALL increased steadily from 10% in the 1960s to about 80% in the late 1980s [7–14]. The COG recently reported analyses of 21,626 patients enrolled in ALL trials between 1990 and 2005 and showed that the 5-year OS increased from 83.7% in 1990–1994 to 90.4% in 2000–2005 ($P < 0.0001$) [15]. Current data (May 2012) show that the 5-year OS is 92.3% for 6,662 patients enrolled in COG ALL trials between 2006 and 2009, which is significantly ($P = 0.0015$) better than OS in the 2000–2005 cohort.

Survival for patients with relapsed ALL remains poor. Prognostic factors for survival post relapse were analyzed in 1961 (of 9,585 total) patients enrolled on COG trials between 1988 and 2002 who relapsed at any site [16]. As previously reported, the major predictors of outcome were time to relapse, site of relapse, and immunophenotype [16–20]. Patients with early BM relapse within 36 months of diagnosis had an abysmal outcome with 5-year OS of about 15% [16].

STATE OF THE DISEASE—BIOLOGICAL

Molecular Targets

Recent studies by the COG and other groups have provided major insights into the genomic landscape of newly diagnosed and relapsed ALL. While a complete description is beyond the scope of this report, these include identification and characterization of the Philadelphia chromosome-like (Ph-like) subtype, discovery of *CRLF2* genomic lesions and JAK mutations, development of molecular risk classifiers, and the identification of key pathways targeted by somatic sequence mutations [21–46]. Large scale whole exome and whole genome sequencing studies currently being performed by the COG and other groups will provide data that should further refine knowledge of the genomic landscape of pediatric ALL and identify new potential biomarkers and therapeutic targets. In parallel, the COG and other groups have analyzed the relationship between host germline variability and ALL incidence, biology, treatment response, and adverse side effects using single nucleotide polymorphism (SNP) arrays [47–54]. The COG has the largest experience in this area with SNP germline genotypes completed for 2,000 patients enrolled in the COG P9900 studies, 2,653 patients enrolled in AALL0232 (86.8% of eligible patients), and an additional 2,000–3,000 genotypes that will be completed in the next few years.

A key finding with major therapeutic implications is the discovery of a subtype called Ph-like (or *BCR-ABL1*-like) ALL that has a gene expression profile similar to that of Ph⁺ ALL, but lacks *BCR-ABL1* fusion [27,29]. Ph-like ALL is three to four times more common than Ph⁺ ALL, and Ph-like ALL patients have a significantly worse 5-year event free survival (EFS) than other HR patients without this phenotype [55]. About 40–50% of Ph-like ALL cases have genomic alterations leading to *CRLF2* over-expression, about half of which have *JAK1* or *JAK2* mutations that are responsive to JAK inhibitors *in vitro* and in xenograft models [22,25,28,32,41,42,56,57]. The COG is conducting a phase I trial (ADV1011) of the JAK inhibitor ruxolitinib, and plans to develop a trial of ruxolitinib combined with chemotherapy in relapsed ALL patients with JAK mutations. COG studies have shown that other kinase gene point mutations occur only rarely in Ph-like ALL [55], but that many Ph-like ALL cases contain fusion genes activating *ABL1*, *JAK2*, and *PDGFRB* that are sensitive to cognate tyrosine kinase inhibitors (TKIs) *in vitro*, in xenograft models, and anecdotally in pediatric ALL patients with lesions such as *EBF1-PDGFRB* fusion [41,42,58]. Based on these findings, the COG is developing technologies to identify patients enrolled in with such fusions with the goal of treating patients with *ABL1* and *PDGFRB* fusions with ABL/ PDGFRB class TKIs.

There are several other molecular targets with therapeutic potential that the COG has or will study. AALL0631 is testing whether the FLT3 TKI lestaurtinib can improve outcome of

infants with *MLL*-R ALL. AALL1122 is the third COG trial of TKI (dasatinib) + chemotherapy in Ph⁺ ALL. Monoclonal antibodies and immunoconjugates are also attractive agents to test in ALL. The COG ADVL04P2 phase II study of epratuzumab + chemotherapy in relapsed ALL did not pass the pre-defined screening benchmark for activity; however, improvements in early MRD response were observed. The bispecific T cell engager agent blinatumomab is an antibody construct that directs CD3⁺ cytotoxic T-cells to CD19 expressing leukemic blasts. Very promising responses have been seen with this agent in relapsed adult ALL and the COG is currently collaborating with international colleagues to conduct a phase I/II trial (AALL1121) of blinatumomab in children with second or greater relapsed or refractory ALL, with plans to test this agent in first relapse of ALL in the near future.

MAJOR RESULTS FROM RECENT COG ALL TRIALS

Prior to the development of TKI therapy, Ph⁺ ALL was one of the worst prognostic groups in pediatric ALL. Despite treatment with intensive chemotherapy and widespread use of allogeneic stem cell transplantation (SCT) less than half of patients survived [59,60]. COG AALL0031 incorporated imatinib, starting after completion of Induction therapy, into a very intensive chemotherapy regimen [61]. The chemotherapy + imatinib regimen was well tolerated, with no significant increased toxicity attributable to imatinib. Patients treated with continuous imatinib (340 mg/m²/day) therapy had a 3-year EFS of 80% versus 35% ($P < 0.0001$) for historical controls treated in the pre-TKI era. COG AALL0622 then tested dasatinib (60 mg/m²/day) + the AALL0031 chemotherapy backbone. Enrollment to this study was completed in February 2012, so mature outcome data are not yet available. Continuous dasatinib treatment (starting on Day 15 of Induction) combined with intensive chemotherapy was determined to be safe based on pre-defined criteria. In AALL0031 continuous imatinib treatment during the last year of maintenance therapy was associated with unacceptable elevation in liver transaminases, so imatinib was given on a 2-week on to 2-week off schedule during this phase [61]. Longer follow-up of AALL0622 is needed to see if continuous dasatinib treatment will be feasible throughout maintenance. AALL0622 patients received dasatinib for the last 2 weeks of Induction and had significantly higher complete remission rates and a much lower proportion of patients were MRD-positive as compared to AALL0031 where TKI was started after Induction [62]. To address the challenge of testing targeted therapies in small, molecularly defined childhood ALL subsets, the COG collaborated with the European EsPhALL group to develop a transatlantic pediatric Ph⁺ ALL trial (AALL1122) of dasatinib + chemotherapy that is now enrolling patients. While the optimal therapy for Ph⁺ ALL remains to be determined, the results of COG AALL0031 have significant implications for other subsets of very high risk ALL and suggest that outcomes can be improved significantly if: (a) a driver molecular lesion is present that is fundamental to leukemogenesis; (b) the leukemia is dependent on continued activity of this molecular lesion (oncogene addiction); and (c) an effective targeted agent is available that can be combined safely with chemotherapy [6]. Recent discoveries of targetable genomic lesions in Ph-like ALL exemplify this approach.

Historically, outcomes for T-cell ALL (T-ALL) have been worse than those for B cell precursor (BCP) ALL [15]. Nelarabine has differential cytotoxicity for T-cell malignancies

and had very promising results in phase I/II trials of children and adults with refractory T-ALL or T-cell lymphoma [63,64]. However, these early phase trials suffered from high rates of serious and sometimes fatal CNS toxicity (Guillain–Barre syndrome, refractory seizures, and coma). COG AALL00P2 established that adding nelarabine to intensive chemotherapy was safe and feasible, with very promising outcomes in children with newly diagnosed T-ALL and high-risk features [65]. This study formed the basis for COG AALL0434, a prospective randomized T-ALL trial of chemotherapy $\pm$ nelarabine that should complete enrollment in 2014.

The COG has taken a different approach than many other groups to treating SR ALL, which comprises about two-thirds of BCP ALL patients. COG trials use a 3-drug (dexamethasone (DEX), PEG-asparaginase (ASNase), and vincristine) Induction without anthracyclines, a 4-week low intensity consolidation phase rather than the intensive 8-week Berlin-Frankfurt-Munster (BFM) or COG augmented BFM (ABFM) consolidation, and no high dose methotrexate (HD MTX). CCG 1991 established that escalating IV MTX without leucovorin rescue was superior to oral MTX during two interim maintenance (IM) phases with almost all of the improvement due to decreased CNS/testicular rather than BM relapses [66]. CCG 1961 showed that a second delayed intensification (DI) phase was not beneficial in HR patients with a rapid response [67] and CCG 1991 had the same finding for SR BCP ALL patients. This more limited treatment approach was highly effective for the ~90% of CCG 1991 SR BCP ALL patients that were good responders based on BM morphology during Induction. The 5-year OS for 2,078 rapid responders was 96.0%; for the ~50% of patients with favorable genetic features (*ETV6–RUNX1* fusion or trisomy 4 + 10), the 5-year EFS and OS were 94.2% and 98.7%, suggesting that a large group of patients can be identified that are almost certain to be cured with relatively limited therapy that includes only 75 mg/m² of cumulative anthracycline exposure and 1 g/m² of cyclophosphamide. This baseline regimen was used in COG AALL0331 (2005–2010) that tested augmented versus standard consolidation (results remain blinded as of September 2012) and the current COG AALL0932 SR-ALL trial.

The COG AALL0232 study was a 2 $\times$ 2 randomized trial that enrolled 3,108 eligible HR BCP patients (2004–2011). All patients received the COG ABFM regimen, which was shown to be superior to the prior standard regimen in CCG 1882 and 1961 [67–69]. Patients were randomized to receive DEX 10 mg/m²/day on Days 1–14 (Dex14) versus prednisone 60 mg/m²/day on Days 1–28 (Pred28) during Induction, and HD MTX with leucovorin rescue versus escalating dose Capizzi MTX without rescue + ASNase during the first IM phase. Patients randomized to HD MTX had superior outcomes to those randomized to Capizzi MTX [70]. The Induction steroid question initially included all patients, but was restricted to those <10 years old in 2008 after interim monitoring showed excess rates of osteonecrosis (ON) among patients 10+ years old randomized to Dex14 [71]. For the patients <10 years, the DH (Dex14 + HD MTX) regimen had superior EFS compared to PH (Pred28 + HD MTX) therapy [72]. In contrast, for patients 10+ years old at diagnosis there was no difference between those randomized to Dex14 versus Pred28. Osteonecrosis rates were much higher in those 10+ years old compared to younger patients, and modest changes in chemotherapy administration significantly impacted ON risk, with interrupted dose DEX

(Days 1–7 and 15–21 vs. 1–21) during DI significantly decreasing ON risk. These results were practice changing; HD MTX and age-based Induction steroid regimens are the new standards of care in COG HR BCP ALL trials.

The COG and CALGB collaborated to compare outcomes for AYA ALL patients 16–21 years old treated on pediatric versus adult cooperative group trials. The AYA patients treated on pediatric trials had dramatically better survival than those treated on the adult trials [73]. Many other groups have reported similar findings [74]. The COG later reported outcome for 262 AYA ALL patients enrolled on CCG 1961 (the largest cohort reported to date) showing 5-year EFS 71.5% and OS 77.5%, establishing that there is no role for routine use of SCT in AYA ALL [75]. Data were recently presented regarding 601 AYA patients 16–30 years old treated on AALL0232, by far the largest group analyzed to date, and showed a significantly increased risk of death in remission for AYA patients as compared to younger HR children in this trial [76,77]. Osteonecrosis is a particular problem among patients 13 years. CCG 1961 established that interrupted dose DEX during DI significantly decreased ON incidence [78]. Parallel genomic studies showed that genetic polymorphisms affect ON risk [47]. To further study risk factors for ON, the current COG HR ALL trial AALL1131 includes pharmacokinetic and genomic studies in parallel with MRI screening.

Despite the use of very intensive therapy, the outcome for infants younger than 1 year with ALL is substantially inferior to that of older children with EFS rates less than 50%, and even lower for the approximately 80% with *MLL*-R [79]. Given these poor outcomes despite highly toxic therapy, COG AALL0631 (2007-present) is testing targeted therapy. Almost all infants with *MLL*-R ALL overexpress the wild type FLT3 TK with evidence of autocrine signaling [80–82]. Pre-clinical studies showed that lestaurtinib, a small molecule FLT3 TKI with excellent oral bioavailability, selectively kills *MLL*-R ALL samples and synergizes with chemotherapy [83,84]. The initial phase of COG AALL0631 has been completed and established that lestaurtinib can be given safely with intensive chemotherapy and has biological activity [85,86]. AALL0631 is now in the efficacy phase with *MLL*-R infants randomized to receive chemotherapy with/without lestaurtinib.

Patients with an early BM relapse occurring within 36 months of diagnosis have a very poor outcome and few survive despite widespread use of SCT [16]. COG investigators hypothesized that it might be possible to increase complete remission (CR) rates and convert more patients to MRD-negative status thereby improving SCT outcomes by adding new agents to an intensive chemotherapy regimen. COG AALL01P2 established the safety of a 3–4 months triple induction regimen consisting of three 4–5 weeks blocks of intensive chemotherapy [87]. COG ADVL04P2 then tested addition of the anti-CD22 monoclonal antibody epratuzumab to this regimen and showed that epratuzumab could be given safely once or twice weekly during the 4-week Induction, but there was no change in CR2 rates with chemotherapy + epratuzumab as compared to historical controls treated with the chemotherapy regimen alone [88,89]. Based on these results, the COG will not pursue epratuzumab further. COG AALL07P1 is now testing addition of bortezomib to the AALL01P2 chemotherapy regimen.

STRATEGIC APPROACH: TARGETED THERAPY

Newly Diagnosed Population

The second generation COG BCP ALL trials (AALL0932/AALL1131) for Ph-negative ALL use a classification and stratification approach (AALL08B1; Table I) whereby SR ALL patients enter AALL0932 and receive a three-drug DEX-based Induction. At end Induction, clinical, genetic, and MRD response data are integrated to assign patients to different studies for post-Induction therapy. AALL0932 patients with adverse genetic features (hypodiploidy, iAMP21, *MLL*-R) or poor response are not eligible to continue on AALL0932, but are eligible to cross over to receive COG ABFM post-Induction therapies with randomized interventions on AALL1131. This approach assures that only patients with an excellent survival (baseline expected 5-year EFS 93%, OS 97%) will be treated with less intensive therapy. In this population, randomized questions are being conducted that focus on maintenance chemotherapy, and embedded studies are assessing health-related quality of life, and physical functioning.

At diagnosis, HR BCP patients enroll in AALL1131 and receive a four-drug Dex14 (1–9.99 years) or Pred28 (10–30.99 years) Induction. At the end of Induction, patients are stratified into HR and very high risk (VHR) subgroups (and AALL0932 HR/VHR patients join these groups) with different randomized interventions on a similar ABFM backbone that utilizes HD MTX during IM#1 for all patients, a single DI phase, and a second IM phase with Capizzi MTX + ASNase (VHR only). The HR group has an estimated 88% baseline 5-year EFS and is randomized to receive intrathecal (IT) MTX versus IT triple chemotherapy. The VHR group includes patients with older age (≥ 13 years), adverse genetics (hypodiploidy, iAMP21, *MLL*-R), or Day 29 MRD $\geq 0.01\%$ and has an estimated 5-year EFS of $\approx 75\%$. Novel therapies are being explored in this group by comparing standard ABFM consolidation/re-consolidation strategies with two different experimental regimens that utilize more myelosuppressive agents commonly used in relapsed ALL, etoposide/cyclophosphamide $\pm$ clofarabine. The 3-drug etoposide/cyclophosphamide/clofarabine regimen has shown significant activity in refractory/relapsed ALL [90–92]. The design of this 3-arm trial will allow the effect of clofarabine to be isolated. Embedded studies assess neurocognitive outcomes using a novel computer-based assessment tool and will define the natural history of ON using serial magnetic resonance imaging.

Because the outcome for T-ALL patients is inferior to that of BCP ALL patients when less intensive treatment is administered [15], all patients with T-ALL are considered high risk and treated with a 4-drug Induction and the COG ABFM backbone. AALL0434 employs a 2×2 design with one intervention testing refinement of standard agents (HD MTX vs. Capizzi MTX + ASNase) and one testing nelarabine.

Relapsed Population

COG AALL07P1 is testing addition of bortezomib to the AALL01P2 triple re-Induction regimen in patients with early BM relapse occurring within 36 months of diagnosis. AALL0433 is designed to see if outcome for patients with late (≥ 36 months) BCP marrow and isolated extramedullary (IEM) (≥ 18 months) relapse, can be improved by using this

same triple re-Induction regimen (without bortezomib) followed by 2 years of intensive chemotherapy.

Trial Design Strategies

Because of the size of patient populations, the COG is able to conduct randomized phase III trials in patients with newly diagnosed ALL, often asking two questions with a 2×2 design. For some small subsets randomizations with relaxed alpha (infant trial AALL0631), or comparison to historical control outcomes (Ph⁺ ALL trials AALL0031/AALL0622/AALL1122) have been used. Recent COG ALL trials for first relapse of ALL have used historical control comparisons in an effort to evaluate new agents more efficiently, but a number of confounding factors such as changes in patient populations or supportive care over time have limited the effectiveness of this approach. Because of this, newly developed COG relapse ALL trials will include concurrent randomizations to control versus experimental arms with novel agents.

KEY TRIALS TO BE PURSUED

Pivotal Phase III Trials

Early relapse is a common cause of treatment failure in T-ALL/T-lymphoblastic lymphoma (T-LL), and patients who relapse rarely survive. These factors suggest that early treatment intensification and early addition of active new agents are needed to improve survival. Pre-clinical data show that bortezomib is active in T-ALL and that it has an additive or synergistic effect with cytotoxic chemotherapy [93–95]. Bortezomib has an acceptable toxicity profile in children, and the COG phase I trial ADVL0317 showed a maximum tolerated dose of 1.3 mg/m² given twice weekly for 2 weeks as a single agent, followed by a 10-day rest [96]. Bortezomib has been incorporated safely into an intensive ALL re-Induction backbone [97,98] and is currently under investigation in ALL patients with early first relapse (AALL07P1). Current plans for the next COG T-ALL/T-LL trial (AALL1231), projected to open when AALL0434 completes accrual in early 2014, are to use a modified COG ABFM regimen (similar to AALL1131) that includes two IM (#1 HD MTX; #2 Capizzi MTX ± ASNase) phases and one DI phase. Based on very promising data regarding DEX efficacy in T-ALL from the AIEOP-BFM 2000 [99] and UKALL 2003 [100] trials, all patients will receive DEX 6 mg/m²/day for 28 days during Induction and two doses of PEG-ASNase given on Days 4 and 18, with a randomization to ± bortezomib 1.3 mg/m² with four doses in Induction and four in DI, using 4-year EFS as the primary endpoint.

To date, the COG has conducted separate trials for the three major risk groups of first relapse ALL (early BM, early IEM, late BM + late IEM). For early BM relapse a series of single arm, limited accrual/duration phase II re-Induction studies have been conducted testing novel agents (ADVL04P2, epratuzumab; AALL07P1, bortezomib) added to the AALL01P2 chemotherapy regimen with the primary endpoint being CR2 rate at end Block 1 as compared to historical control data with chemotherapy alone. COG first relapse trials for intermediate (early IEM) and low (late BM + late IEM) risk patients have each used unique multiagent chemotherapy regimens with or without randomized interventions with 3-year EFS endpoints. To date, MRD response has not been used to allocate subsets of late BM

relapse patients to receive SCT, which is becoming a standard approach. This fragmented approach to relapse trials has been associated with poor accrual that has led to problems in completing studies efficiently. The challenges of executing trials in patients with relapsed LL have been even more problematic. To address these problems and test new agents efficiently in these very high risk populations, COG is developing a comprehensive trial that will include all patients with first relapse of ALL/LL and which will adopt a platform, commonly used in European studies. This approach has been successful in other cooperative groups, including the I-BFM and UK CCLG/Australia/New Zealand consortia [19,101].

Though the design of this comprehensive relapse trial is not yet finalized, it is envisioned that late BCP ALL BM and IEM relapse patients will receive three blocks of a standard chemotherapy backbone that is a slightly modified ALLR3 regimen [101]. These patients will be defined as low (LR; MRD <0.1% end Block 1) and intermediate risk (IR; MRD 0.1% end Block 1) based on early MRD response. The IR patients will not continue to receive treatment on this study after Block 3, but will be eligible for SCT trials developed by the COG SCT and ALL committees. The LR patients will continue on study and receive 2 years total treatment with a post Block 3 randomization to $\pm$ - blinatumomab replacing 16 weeks of conventional chemotherapy. The approach for high-risk patients with early BM relapse of BCP ALL or any BM relapse of T-ALL/LL has not yet been finalized.

Prioritization Strategy

While overall outcomes are excellent for ALL, it remains the single largest cause of cancer related death in children [2]. Even though good risk subsets of newly diagnosed ALL patients now have 5-year OS approaching 95%, 38% of deaths that occurred in patients diagnosed between 1990 and 2005 were in those with good risk clinical features [15]. Thus, it is imperative to conduct randomized trials testing interventions seeking to improve EFS for subsets with less than 95% 5-year EFS. Identification of patients with expected EFS of at least 95% is now possible at end Induction, so it is likely that future COG ALL trials will enroll all patients with ALL at initial diagnosis, with ultralow risk subsets identified at end Induction that will not participate in randomized questions. The current approach is to ask questions focused on refining the use of standard agents in subsets with expected EFS above about 85%, and to test new agents and targeted therapies in subgroups with a worse outcome. As new agents that are effective and have favorable toxicity profiles are identified, it will be important to test them in good risk subsets to see if they can improve outcome for these patients and/or replace cytotoxic chemotherapy agents associated with adverse short/long term toxicities.

National and International Collaborations in Childhood ALL

As the number of relapses decreases for childhood ALL, national and international collaborations are increasingly required to further improve survival. The major North American (including COG, the Dana Farber Cancer Institute consortium, and St. Jude Children's Research Hospital), European and Asian childhood ALL treatment groups form the Ponte di Legno Childhood ALL collaborative network and leaders meet periodically to discuss trial results, trial design strategies, and to plan collaborative research projects on rare patient subsets [102]. These collaborations have provided important insights into high-risk

subsets with recent major publications on hypodiploid ALL, Ph⁺ ALL, Induction failure, and near final manuscripts on Down syndrome-ALL and second malignant neoplasms in patients treated for ALL [60,103,104]. Because of these ongoing interactions, the groups have become comfortable sharing unpublished data to facilitate design of new trials by other groups. Critically, international collaboration will be required to test new targeted therapies in relatively uncommon (<5–10% of childhood ALL), molecularly defined patients subsets that have a poor outcome, as exemplified by the current international Ph⁺ ALL trial (COG AALL1122).

CONCLUSIONS

Cure rates for pediatric ALL are outstanding, but ALL remains the leading cause of childhood cancer death. Optimization of conventional chemotherapy has improved outcome for favorable risk subgroups, but has had limited effect for poor risk subgroups of newly diagnosed and relapsed ALL. Targeted therapy has revolutionized treatment of Ph⁺ ALL and provides a roadmap for how to approach other poor risk subgroups. Current and future COG ALL trials will focus on using existing and newly discovered biomarkers to stratify patients into different risk groups and testing novel agents and treatment strategies for those predicted to have a poor outcome. With decreasing relapse rates and improving survival, enhancements in supportive care to decrease morbidity and mortality and better measures of short- and long-term quality of life become even more important. Parallel translational research efforts have led to major new insights into ALL biology, host polymorphisms associated with ALL occurrence, genotype, response, and toxicities, and identified new biomarkers and potential therapeutic targets. Emerging data from large-scale next generation sequencing studies should identify additional therapeutic targets to pursue in COG ALL clinical trials.

Acknowledgments

This work was supported by the Chair's grant U10 CA98543, Statistics and Data Center grant U10 CA98413, CCOP U10 CA95861, Human Specimen Banking U24 CA114766 grants of the Children's Oncology group from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. A complete listing of grant support for research conducted by the Children's Cancer Group and Pediatric Oncology Group before initiation of the COG grant in 2003 is available online at: <http://www.childrensoncologygroup.org/admin/grantinfo.htm>. Stephen Hunger is the Ergen Family Chair in Pediatric Cancer.

Grant sponsors: National Cancer Institute; National Institutes of Health, Bethesda, MD.

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TABLE I

Overview of the AALL08B1 Classification System for B-Precursor ALL

Risk group	Low		Average ^d		High ^b		Very high		
Projected 5-year EFS	>95%		90–95%		88–90%		<80%		
NCI risk-group	SR	SR	SR	SR	SR	SR	HR	HR (13 years)	SR or HR
Favorable genetics ^c	Yes	Yes	No	Yes	No	No	Any	Any	Any
Unfavorable characteristics ^d	No	No	No	No	No	No	No	No	Yes
Day 8 PB MRD	<0.01%	0.01%	<1%	Any	1%	Any	Any	Any	Any
Day 29 BM MRD	<0.01%	<0.01%	<0.01%	0.01%	<0.01%	<0.01%	0.01%	<0.01%	Any
Accrual/year	250	350	266	70	89	264	64	154	116
Total accrual/year	250	616		423		413		24.3%	
Fraction of patients	14.7%	36.2%		24.8%		24.3%			

SR, standard risk; HR, high risk; PB, peripheral blood; MRD, minimal residual disease; BM, bone marrow.

^aNCI SR patients who are CNS2 may be included in average risk, but will not be eligible for the low risk Arm.

^bAll patients with testicular leukemia will be assigned as HR at start Induction, but may change to VHR if Day 29 MRD 0.01% or unfavorable characteristics are present.

^c„Yes” is defined as the presence of double trisomy 4 and 10 OR *ETV6–RUNX1* fusion.

^dConsists of patients with CNS3, hypodiploidy (<44 chromosomes and/or DNA index <0.81), iAMP21, Induction failure (M3 marrow Day 29), or *MLL* rearrangement (not *MLL* deletion). *BCR–ABL1* positive patients are eligible for a separate Ph⁺ ALL study.