Title: RISK AND RESPONSE-BASED CLASSIFICATION OF CHILDHOOD B-PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA: A COMBINED ANALYSIS OF PROGNOSTIC MARKERS FROM THE PEDIATRIC ONCOLOGY GROUP (POG) AND CHILDREN'S CANCER GROUP (CCG).

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ABSTRACT

The Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) joined to form the Children's Oncology Group (COG), in 2000. This merger allowed analysis of clinical, biological, and early response data predictive of event-free survival (EFS) in acute lymphoblastic leukemia (ALL) to develop a new classification system and treatment algorithm. From 11,779 children (1 to 21.99 years) with newly diagnosed B-precursor ALL consecutively enrolled by the CCG (December 1988 to August 1995, N = 4986) and POG (January 1986 to November 1999, N = 6793), we retrospectively analyzed 6238 patients (CCG 1182, POG 5056) with informative cytogenetic data. Four risk groups were defined as very high risk (VHR, 5-year EFS ≤45%), lower risk (5-year EFS ≥85%) and standard and high risk as those remaining in the respective NCI risk groups. VHR criteria included extreme hypodiploidy (<44 chromosomes), t(9;22) and/or BCR-ABL, and induction failure. Lower risk patients were NCI standard risk with either t(12;21) (TEL-AML1) or simultaneous trisomies of chromosomes 4, 10, and 17. Even with treatment differences, there was high concordance between the CCG and POG analyses. The COG risk classification scheme is being used for division of B-precursor ALL into lower (27%), standard (32%), high (37%), and VHR (4%) risk groups based on age, WBC, cytogenetics, day 14 marrow response and end induction MRD by flow cytometry in COG trials.
BACKGROUND

The treatment of childhood ALL has advanced significantly over the past three decades with overall survival rates progressing from 20% to 75%. This improvement can be attributed, in part, to intensification of therapy using agents previously shown to be effective in the treatment of ALL. While this approach has improved overall EFS it is clear that a number of patients might have been cured with less aggressive therapy. However, patients identified at diagnosis as having better risk features still account for the majority of relapses. In an effort to appropriately balance the risks and benefits of therapy, “risk adapted therapy” has been adopted. EFS is predicted based on clinical and biological variables, and treatment intensity is then modified according to expected EFS, to maximize cure while minimizing toxicity.  

The Pediatric Oncology Group (POG) and Children’s Cancer Group (CCG) adopted a common set of risk criteria in 1993 at an international conference supported by the NCI. The NCI criteria were based on factors that had international acceptance and reproducibility: age, initial white blood cell (WBC) count, and the presence of extramedullary disease at diagnosis. To further refine therapy, both POG and CCG have also utilized additional risk factors that have been shown to have an impact on patient outcomes (e.g. ploidy, blast karyotype, and early morphologic response). Recently, the POG and CCG merged to form the Children’s Oncology Group (COG). This merger provided an opportunity to reassess individual approaches and develop a consensus classification strategy for treatment assignment. A COG ALL risk classification subcommittee developed a classification system that was: a) optimal for patient care; b) amenable to asking biologic and therapeutic questions, and; c) functional, so that risk
directed therapy could be offered to all eligible patients, regardless of geographic location. This analysis included the clinical and biological variables utilized in each legacy group such as age, WBC, gender, extramedullary disease, blast cytogenetics and ploidy, and early response to therapy. The resulting classification system incorporated the strongest prognostic indicators predictive of outcome in both groups, despite marked differences in treatment strategies and delineated four risk groups with different outcomes. This paper presents the results of these analyses and the basis of the current classification system for COG ALL trials.
MATERIALS AND METHODS

Criteria for selection of risk factors

Variables were selected for inclusion in the final COG risk algorithm if both POG and CCG data revealed a strong correlation between the variable and outcome. A prognostic factor could also be selected for inclusion if there was a strong correlation within one of the two cooperative groups with limited correlation shown by the other group, or through published literature. A second set of variables were excluded from the current COG ALL risk algorithm, but were identified for further study (and validation), if there was a strong prognostic effect within one of the two groups with no published support or confirmation by the other group. Since data regarding the influence of minimal residual disease (MRD) on outcome were not available from the CCG or POG trials, we relied on published data to establish a level of MRD that would impact classification and protocol assignment.

Patients and Treatment:

The patients studied were children (ages 12 months to 21.99 years) with newly diagnosed B-precursor ALL consecutively enrolled on CCG (December 1988 to August 1995) and POG (January 1986 to November 1999) protocols. Eligibility for analysis in the current study for CCG patients included enrollment on CCG 1881, 1882, 1891, 1901, and 1922 for patients with B-lineage ALL or no assigned immunophenotype and with informative cytogenetics as defined below. POG patients included in these analyses were those enrolled on the ALinC 14 (POG 8602), ALinC 15 (POG 9005, 9006), and ALinC 16 (POG 9201, 9405, 9406, 9605) protocols for B-precursor ALL. Only patients with designated B-precursor immunophenotyping and with informative leukemic cell cytogenetic results were used in the analyses. Analyses for the
presence of the TEL-AML1 translocation or trisomies of chromosomes 4, 10 and 17 and impact of combined day 7 and 14 marrow response and outcome were performed on a later data set from CCG protocols 1952 for NCI standard risk (1996-2000) and 1961 for NCI high risk (1996-2002), since these data were not available in the original data set. The details of each protocol can be obtained from published reports.6-18 In general, CCG studies utilized reinduction/reconsolidation pulses modified from the Berlin-Frankfurt-Muenster (BFM) clinical trials consortium with further modifications in the augmented regimen14, while POG protocols employed antimetabolite-based pulses, emphasizing the use of ”intermediate dose” (1 gram/m² given intravenously over 24 hours) methotrexate with leucovorin rescue. All protocols were approved by the NCI and by the Institutional Review Board (IRB) of each participating institution. Informed consent was obtained from the patients and/or families prior to enrollment.

**Diagnosis:**

**CCG:** The diagnosis of ALL was based on morphologic, cytochemical and immunologic features of the cells, including lymphoblast morphology on Wright-Giemsa-stained bone marrow smears, positive nuclear staining for terminal deoxynucleotide transferase (TdT), negative staining for myeloperoxidase, and cell-surface expression of two or more B cell-precursor lymphoid differentiation antigens. Immunophenotyping was performed centrally in the CCG ALL Biology Reference Laboratory by indirect immunofluorescence and flow cytometry. In some early trials no centrally performed immunophenotyping information was available for a proportion of patients. Patients were classified as B-lineage if ≥ 30% of their leukemic cells were positive for CD19 or CD24 and if < 30% of their leukemic cells were positive for one or more of the T-cell associated antigens for CD2, CD3, CD5, or CD7.
**POG:** Diagnostic criteria included cytochemical stains and morphology consistent with ALL and reference laboratory immunophenotyping consistent with B-precursor ALL as defined in the previous section for CCG patients.

**Clinical and Laboratory Variables Used to Risk Stratify Patients in Legacy Studies:**

Both CCG and POG assigned preliminary risk group for induction therapy according to the NCI-Rome risk group definitions of standard risk (age < 10 years, and WBC count < 50,000/uL) and high risk (one or more of the following: age ≥ 10 years, WBC count ≥ 50,000/uL). Infants < 1 year of age were not included in the current analyses. Additional variables assessed include gender, hepatosplenomegaly, lymphadenopathy, and presence or absence of extramedullary disease at diagnosis. CCG measured early response by evaluating bone marrow morphology on day 7 and/or day 14 of induction therapy. Conventional morphologic criteria were used to assess blast content in these hypocellular marrows: M1 < 5% blasts, M2 5% to 25% blasts and M3 > 25% blasts. CNS-3 disease was defined as ≥ 5 nucleated cells/microliter with ALL blasts detected by cytospin. CNS-2 was defined as the presence of blasts by cytospin in CSF with < 5 nucleated cells/microliter and CNS1 as any number of nucleated cells per microliter with no ALL blasts detected by cytospin. Patients enrolled on the legacy POG ALineC 15 study were further risk classified at the end of induction based on DNA index and the presence of the t(9:22) or t(1;19). On the POG legacy study ALineC 16, modification of the initial NCI risk grouping was defined at end of induction as follows: Trisomies 4&10 (or DI >1.16 if cytogenetic studies not informative) promoted NCI standard risk
to good risk and NCI high risk to standard risk. Any patient with CNS-3 or testicular disease or t(1;19), t(4;11), or t(9;22) was assigned to the poor risk group.

**Cytogenetic Analysis:**

Analysis of bone marrow or unstimulated peripheral blood specimens obtained prior to initiation of remission induction therapy was evaluated according to standard protocols by CCG institutional and POG reference laboratories. Criteria for clonality were based on guidelines as defined by International System for Cytogenetic Nomenclature (i.e. two or more metaphase spreads with identical structural or additional chromosomes or three or more metaphases with identical chromosome loss). Members of the respective CCG and POG Cytogenetics Committees reviewed the cytogenetic reports, together with representational karyotypes, for each abnormal clone. Cytogenetic analyses were considered informative, if after review, an abnormal clone was identified or analysis of bone marrow karyotype revealed a minimum of 20 normal cells.

**CCG and POG Patient Populations**

From a total of 4986 eligible, non-infant patients with ALL treated on CCG protocols open from 1988 – 1995, 3056 (61.3%) had evaluable immunophenotyping data, and 1182 (38.7%) of those 3056 patients had evaluable cytogenetics (Figure 1). There are no significant differences in outcome between the total patient population of 4986 patients (5-year EFS 76.2%), and the subset of 3056 with evaluable immunophenotype data (5-yr EFS 75.9%) and the subgroup of 1182 with both evaluable immunophenotyping and cytogenetic data used for detailed analyses in this report (76.0%) (Table 1). Of a total of 6793 eligible patients (5-yr EFS 73.6%) enrolled on
POG protocols from 1986-1999, 6780 (99.8%) had evaluable immunophenotype data (5-yr EFS 73.6%) and 5056 (74.6%) of these (5-yr EFS 73.0%) had evaluable cytogenetic data and were used for detailed analyses in this report. Eleven of the 5056 POG patients (NCI Standard risk: 3516, NCI High Risk: 1529) could not be classified into a NCI risk group due to missing WBC at diagnosis, and were not included in any analyses by NCI risk group, although included in the overall analyses. There appeared to be no selection bias with similar outcomes in the total groups and the analyzed subgroups.

Statistical Methods:

The primary outcome considered was event-free survival (EFS) calculated as the time from entry on a therapeutic trial to first event or date of last follow-up, where an event was defined as: induction failure, relapse at any site, secondary malignancy, or death. Patients who did not fail were censored as of the date of last contact. Event-free survival curves were constructed using the Kaplan-Meier life table method. Standard deviations of the Kaplan-Meier estimates were based on the Peto variance estimates for the life table curves. The log-rank test was used for comparison of survival curves between groups.
RESULTS

Identification of a very high risk group

In order to identify a very high risk subgroup for alternative therapies such as blood and marrow transplantation (BMT), we evaluated the entire cohort to identify factors associated with a projected 5-year EFS $\leq 45\%$ on previous POG and CCG protocols. Data on the occurrence of the $BCR/ABL$ translocation (by karyotype, RT-PCR or FISH) are summarized in Table 2. Children with $BCR/ABL$ or $t(9;22)$ treated on POG or CCG protocols had overall 5-year EFS rates of 27.4% and 33.3%, respectively. Older age and higher WBC (NCI high risk) have been associated with poorer prognosis as compared to NCI standard risk in Ph+ ALL. This was confirmed in POG Ph+ patients with 18.2% five-year EFS for high risk compared to 52.4% for standard risk patients (Table 2).

Patients with hypodiploidy (<45 chromosomes) had a 5-year EFS of 46.5% for POG and 35.7% for CCG (Table 2). There was no significant effect of either WBC or age in the marked hypodiploid patients. In our initial analysis, patients with hypodiploidy defined as <45 chromosomes were classified as very high risk; however, as described in the discussion, more recent data from a large international collaboration demonstrate that leukemias with 44 chromosomes are associated with an intermediate prognosis, and those with < 44, a poor prognosis.
A third variable associated with very high risk was failure to achieve remission at the end of induction therapy. Induction failure was defined as either an M3 (>25% blasts) response in the BM at the end of induction (CCG and POG) or an M2 (5 – 25% blasts) marrow at the end of induction followed by ≥5% blasts (M2/3) at the end of extended induction (POG) or consolidation therapy (CCG). The relative frequencies of an M3 bone marrow at end of induction were 1% and 0.1% among high risk and standard risk patients, respectively on CCG studies. Detailed analysis of this data set was limited since patients were removed from protocol therapy once they had failed induction, specific treatment data were not collected and, we were unable to make exclusions based on immunophenotyping and cytogenetics. There were 41 patients with an M3 marrow at the end of induction with 29 (70%) achieving remission after additional therapy. Of this group, 18 received a BMT (type indeterminate) and 11 received chemotherapy. The 5 year DFS for this CCG patient group was 44% overall with the BMT group performing better than the chemotherapy group (52.6% versus 33.3%). Of those failing to achieve a remission after additional therapy, all died within 9 months. On the POG studies, the overall induction failure rate was 1.3%. No data on subsequent therapy or relapses were captured on POG studies for induction failures, making analysis of later outcome impossible.

**Analysis of other potential very high risk features**

Other factors have been associated with a high risk of relapse in prior studies, including *MLL* rearrangements,24,25 monosomy 7,26 a balanced t(1;19) translocation,27 WBC >200,000/µL and age >15 years.28 POG and CCG molecular data documenting *MLL* rearrangements were limited. The incidence of t(4;11) among B-precursor ALL patients >12 months of age at diagnosis, was about 1%. Patients with t(4;11) had a poor prognosis (Table 3) but did not meet
the criteria for the very high-risk group (≤45% 5-year EFS). Evaluation of the impact of slow early response (SER) in patients treated on CCG 1961 (1996 – 2002) demonstrated that patients with t(4;11) and an M3 marrow at day 7 had an extremely poor prognosis with 1 of 9 remaining in first remission. Patients with other 11q23 abnormalities did not have a poor prognosis.

Previously, the t(1;19) (q23;p13) has been reported to be an adverse prognostic factor and the CCG has reported that a balanced t(1;19) translocation was associated with significantly worse prognosis than the unbalanced variant. In our current analysis of outcome on CCG trials, patients with a balanced t(1;19) had a 5-year EFS of 50% vs. 81.8% for patients with an unbalanced t(1;19) (Table 3) but it was based on only 51 t(1;19) patients and 18 with the balanced t(1;19). Analysis of 273 patients with a t(1;19) treated on POG trials showed no significant outcome difference between those with the balanced (68.2%) or unbalanced (74.1%) variant. Thus, t(1;19) was not included in the risk stratification algorithm.

Other variables including race, gender, age > 15 years, and WBC > 200,000/uL (Table 4) were evaluated to determine if these features defined a very high risk group. These comparisons included only NCI high risk patients. When each factor was considered individually, POG patients with a WBC >200,000 had a 5-year EFS of 38.6 %, but this was not confirmed by CCG data.

The impact of central nervous system (CNS) disease at the time of diagnosis was analyzed. CNS-3 and CNS-2, NCI standard risk POG patients had a 5-year EFS of 71.8% and 70.1%, respectively, compared to 79.9% for CNS-1 (Table 4). NCI high-risk POG patients had a
similar trend with a 5-year EFS of 58.7% and 59.0% among CNS-3 and CNS-2 patients, respectively, compared to 64.0% for CNS-1 (Table 4). In CCG studies, only CNS-2 patients had a lower 5-year EFS (67.0%), with EFS in CNS-1 and CNS-3 patients of 78.4% and 76.2%, respectively. Only 18 patients were diagnosed as having testicular disease at diagnosis, precluding meaningful analysis.

**Conventional measures of early marrow response to therapy**

Rapidity of response was used to identify patients for treatment intensification on CCG trials based on the presence of a slow early response (SER), defined as an M3 bone marrow on day 7 (high risk) or an M2/3 marrow on day 14 (standard risk) of induction. The CCG trials included in the primary analyses in this report determined either day 7 or day 14 marrow response, not both. We analyzed data from B-precursor ALL patients enrolled in CCG 1952 (standard risk) and CCG 1961 (high risk) in which a day 7 marrow response was determined and had a day 14 marrow response assessed if the day 7 marrow was not M1 (approximately half of patients). Evaluation of NCI high-risk patients treated on CCG 1961 showed that both day 7 SER (M3) and day 14 M2/M3 patients had an inferior outcome, even though patients with a day 7 M3 marrow were non-randomly assigned to augmented therapy (Table 5). Similarly, early response was a strong predictor of outcome among standard risk ALL patients treated on CCG 1952 with SER patients, defined as a day 14 M3 marrow, (who were non-randomly assigned to augmented therapy) having an inferior outcome to those with an RER (5-year EFS 66.5% vs. 84.4%). Rapid response to induction therapy was also an important predictor of outcome in patients with the presence of favorable features, including \( TEL/AML1 \) fusion or trisomies of chromosomes 4, 10, and 17 (data not shown).
Identification of a lower risk group

Patients with a lower risk of relapse were defined as those having a 5-year EFS of $\geq 85\%$. Hyperdiploidy is associated with an improved survival although, more recently, specific chromosome trisomies are more important than ploidy (as determined by chromosome number or DNA index).\textsuperscript{32,33} POG previously reported that the combination of trisomies 4 and 10 was associated with a good prognosis.\textsuperscript{6} CCG had identified trisomies 10, 17, 18 as each independently prognostic with the best prognosis associated with both trisomies 10 and 17.\textsuperscript{32} Recently, evaluation of CCG and POG patients using identical methodology showed that simultaneous trisomy of chromosomes 4, 10, and 17 (“triple trisomies”) was associated with an excellent prognosis.\textsuperscript{34} Patients in the NCI standard risk group with triple trisomies had a 5-year EFS of 89.3\% in POG and 91.5\% for CCG (Table 6).

Previously, the cryptic t(12;21) \textit{TEL/AML1} fusion, first reported in 1995,\textsuperscript{30,31} was associated with a very good outcome. \textit{TEL/AML1} fusion was assessed in only a subset of patients treated on more recent trials reflecting the smaller numbers and limited duration of follow-up compared to the other analyses performed for this manuscript. The 5-year EFS of NCI standard risk patients with \textit{TEL/AML1} fusion on POG protocols 9201, 9405, and 9605; and CCG protocol 1952 was 85.1\% and 86.2\%, respectively (Table 6).

A risk assignment algorithm for B precursor ALL

Using the previous analyses and emerging data from other studies, a classification system was developed and implemented as COG AALL03B1 (\textit{Classification of acute lymphoblastic
leukemia). The algorithm utilizes a number of biological markers, some of which are determined at each COG center and others at central COG laboratories. The algorithm initially classifies patients and assigns induction chemotherapy as either NCI standard (3-drug induction) or high risk (4-drug induction) based on age and presenting white blood cell count. At the end of induction therapy, risk stratification is refined based on biologic features of the leukemia (the presence of extramedullary disease, ploidy, triple trisomies, TEL/AML1 or BCR/ABL fusion) and early treatment response (day 15 and 29 morphology determined at local centers, and day 29 MRD determined at COG reference laboratories by flow cytometry) to assign patients into lower (Figure 2a), high (Figure 2b), standard and very high (Figure 2c) risk subgroups. The predictive ability of the COG ALL risk classification algorithm is illustrated with the later CCG (CCG 1952 standard-risk, 1961 high-risk) trials in Figure 3a and POG (POG 9201 lower risk, 9405 standard-risk, 9406 high-risk, and 9605 standard-risk) trials in Figure 3b.
Discussion

This study, designed to identify prognostic factors from the most recent era of completed CCG/POG clinical trials, includes over 6000 children with newly diagnosed B-precursor ALL. This represents the largest reported ALL prognostic factor analysis in children to date allowing for the validation of a number of markers previously identified in smaller analyses. This large number of patients has allowed for the limited analyses to identify smaller risk groups and is unique in that it was performed on patients receiving different approaches to ALL therapy. Treatment on CCG studies was based on modifications of the BFM treatment regimen with re-induction/reconsolidation courses (“delayed intensification”), with further intensification in patient subsets (“augmented” therapy)\(^{14}\). The POG protocols were predominantly antimetabolite-based, with intensification using intermediate dose Methotrexate and no delayed intensification phases. One major difference between the two groups was the extensive utilization of central reference laboratories by the POG, resulting in a higher percentage of available cytogenetic and/or molecular analyses and providing larger patient numbers for the current analyses. Another major difference between the two groups was the use of distinct protocols for T-cell and B-precursor ALL by the POG compared to common protocols by the CCG. The latter difference was not a factor, since we limited to analyses to B-precursor ALL. In our analyses, age and WBC remained important variables in trials conducted by both groups. In contrast, other variables previously predictive of outcome including gender, race, hepatosplenomegaly, mediastinal mass and FAB morphology have been replaced by genetic analyses of the leukemic blast and evaluations of early treatment response.

In spite of different approaches by POG and CCG, there were striking consistencies among certain prognostic factors suggesting underlying biological features that mediate treatment
outcome. Both groups demonstrated that Ph+ ALL and extreme hypodiploidy were very poor risk factors and that TEL/AML1 fusion and triple trisomies conveyed a very good prognosis. Originally patients with <45 chromosomes or a DNA index of less than 0.81 were classified in the very high risk group, but an analysis of a large international cohort revealed that only hypodiploid pts with < 44 chromosomes had a very poor outcome. Subsequently, additional international analyses of larger groups of hypodiploid patients, including these COG ALL patients, found that patients with ≤43 chromosomes had a very poor prognosis, while those with 44 or 45 chromosomes did not (EFS > 45%). Based on this, we modified our definition of extreme hypodiploidy for inclusion in the very high risk group to less than 44 chromosomes or a DNA index of less than 0.81. In our initial analysis, 11q23 translocations alone or the t(4;11) in particular did not meet criteria for very high risk. However, based on the outcome of t(4;11) patients with a SER in CCG 1961, we expanded our definition of very high-risk patients to include those with an 11q23 (MLL) translocation and a poor response to induction chemotherapy. More effective therapy appears to have negated the prognostic importance of t(1;19)(q23;p13) or a balanced t(1;19).

There were some outcome differences between the two cooperative groups. For example, NCI high risk patients with CNS3 disease at diagnosis treated on CCG trials had a 10 – 15% better 5-year EFS than on POG trials. However, with relatively small number of patients, definitive conclusions could not be drawn. CNS2 status at diagnosis in both groups was consistently worse than that of CNS1 patients, and no better than CNS3 patients. Since CNS3 patients received cranial irradiation and CNS2 patients did not, CNS-directed therapy should be considered for CNS2 patients in future trials.
Early response based on bone marrow morphology has been consistently reliable in predicting outcome\textsuperscript{36,37} and augmentation of therapy for poor early response has had a major impact on outcome. CCG-1882 randomized SER patients (M3 day 7) to receive standard treatment or an augmented regimen resulting in a significantly better outcome (5-year EFS of 74 +/- 3.8% vs. 55 +/- 4.5%)\textsuperscript{14}. Similar findings, based on the results of a day 14 bone marrow, were seen in standard risk patients treated on CCG-1952. In CCG-1952, patients with an M3 marrow at 14 (M3/M3) received augmented therapy, while patients with M2 at Day 14 (M3/M2) received standard therapy. The CCG-1952 data demonstrate that the outcome for the M3/M3 patients (augmented therapy) was significantly better than that of the M3/M2 patients (standard therapy)\textsuperscript{38}. Thus, morphological assessment of tumor burden continues to play an important role in the current classification system. In current COG trials, patients with NCI high or standard risk ALL are considered to be SER if the day 14 bone marrow is M2 or M3. SER patients who do not meet criteria for the very high-risk group will receive the augmented BFM regimen regardless of their initial NCI risk classification. Uniform use of the day 15 marrow was selected as it separates patients with greater specificity into groups with a 5-year EFS that is 15-20% lower than with RER (Table 5).

A major recent advance in childhood ALL therapy has been the development of tools to measure subclinical levels of MRD. The clinical trials used for the analyses in this report did not include MRD determinations. While data were not mature enough for outcome analysis at the time we designed the current generation of COG trials, the ongoing POG 9900 generation of trials had established the feasibility of real time MRD determination via flow cytometry in a central reference laboratory. In the >3,000 patients enrolled on POG 9900, informative MRD
results were available for >95% of patients within 24 hours of sample receipt. With no mature POG or CCG MRD data available to construct the ALL classification system, we relied on published data that demonstrated a strong correlation between end induction MRD and outcome, using either flow cytometric or molecular techniques. Patients with low-end induction MRD burden (≤10^{-3} to 10^{-4}) have an excellent outcome, compared to a high end induction MRD burden (> 10^{-2}) having a poor outcome^{39}. In the COG classification scheme (AALL03B1), we included both early morphologic response and end induction MRD levels. Patients are defined as SER if the day 15 marrow contains ≥5% blasts by morphology (M2 or M3) or if the day 29 MRD burden is ≥0.1%. Such patients are non-randomly assigned to receive the “augmented BFM (A-BFM)” regimen that has been shown to improve the outcome of patients with a poor early marrow response in CCG 1882^{14}. Patients with either an M2 marrow or ≥1% MRD by flow cytometry at day 29 receive two additional weeks of extended induction chemotherapy followed by response assessment. The continued use of an extended induction for M2 or MRD positive patients has been maintained since both POG and CCG utilized additional post induction therapy in previous protocols.

The current analysis of almost 6,000 children and adolescents with ALL has provided an unprecedented opportunity to create an algorithm for identifying prognostic patient groups. The application of this algorithm (Figure 2 a, b, c) for risk classification, in current cooperative group trials, will divide patients with B-precursor ALL into low risk (about 27% of the total), standard risk (32%), high risk (37%) and very high risk (4%) groups. This classification scheme balances the risks and benefits of intensified therapy by selecting patients who have a higher risk and will benefit most from treatment intensification and facilitates identification of VHR patients, who
are candidates for experimental therapy. Because our analyses did not identify a group with > 95% expected EFS, the current generation of COG ALL trials asks randomized questions of treatment intensification in low, standard and high risk groups, on therapy backbones of different intensity. With the exclusion of patients with CNS2 disease and the addition of MRD criteria in the classification algorithm we expect to identify low risk patients with a > 95% chance of cure, who might be candidates for a reduction of therapy question in future COG ALL trials.

After initial NCI risk classification, the COG end induction risk stratification algorithm requires immunophenotypic and molecular cytogenetic data as well as early response data which must be available by day 35 of induction. In the current risk stratification schema, COG B-precursor ALL patients groups with varying prognoses are assigned to induction therapies according to data identified at the local center: age, initial WBC count, and immunophenotype. After blast genotype and early response criteria become available, in conjunction with data on the presence of extramedullary disease, patients are risk assigned to different post-induction therapies and randomized questions. Patients with NCI standard risk ALL are subdivided into standard risk-low, standard risk-average and standard risk-high groups (Figure 2a). Standard risk-low and -average patients are eligible for randomization whereas standard risk-high patients are non-randomly assigned to the most augmented regimen in that study. NCI high-risk patients with an SER, CNS or testicular disease are non-randomly assigned to the augmented arm of that study, with all others randomized (Figure 2b). Very high risk patients, identified at the end of induction, include those with Ph+ ALL, severe hypodiploidy, MLL translocation with an SER, and induction failures from all risk groups (Figure 2c). All are eligible for the COG VHR ALL
trial, starting at the end of induction, that includes aggressive chemotherapy, HLA-matched sibling donor BMT, and, for Ph+ ALL, the BCR/ABL kinase inhibitor, Imatinib.

The COG risk stratification algorithm requires an intensive evaluation for clinical, immunophenotypic, cytogenetic and molecular markers with a rapid turnaround for risk classification and protocol assignment. COG expanded the POG reference laboratory classification system to include two additional central reference laboratory for cytogenetic, molecular, immunophenotyping and MRD analyses with sample analysis of 2000 ALL patients per year from over 230 COG centers in the United States, Canada, Australia, New Zealand, and Western Europe. These population based data sets, inclusive of patients regardless as to geographic location or socio-economic status, allow for ongoing analysis of the factors described in this paper and other potential markers. For example, monosomy 7 may confer a poor prognosis. The current generation of COG ALL clinical trials will assess the relative importance of prognostic variables with shared treatment arms on the low risk, standard risk and high risk studies to allow for the determination of end induction MRD in the context of variables like blast genotype (e.g. TEL/AML1). The application of this strategy may be of limited use to either single centers or smaller cooperative groups that do not have adequate resources.

Many of the current risk assessment variables are imprecise surrogate markers for underlying biological factors of the host and blasts. The COG is using newer technologies to examine blast gene expression profiles and host gene polymorphisms that may provide better predictive tools and lead to a mechanistic understanding of treatment success or failure. Since individual biologic and clinical factors are dependent on the therapy delivered, further
therapeutic optimization may result in factors losing their prognostic impact, underscoring the importance of ongoing assessment.
<table>
<thead>
<tr>
<th>Group</th>
<th>NCI Risk Group</th>
<th>N</th>
<th>5 Year EFS (SE)</th>
<th>8 Year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POG</td>
<td>CCG</td>
<td>POG</td>
<td>CCG</td>
</tr>
<tr>
<td>All eligible¹</td>
<td>Any</td>
<td>6793²</td>
<td>3056</td>
<td>73.6(0.7)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>4740</td>
<td>2019</td>
<td>79.1(0.7)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>2040</td>
<td>1037</td>
<td>60.9(1.4)</td>
</tr>
<tr>
<td>All eligible with evaluable cytogenetics⁴</td>
<td>Any</td>
<td>5056³</td>
<td>1182</td>
<td>73.0 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>3516</td>
<td>776</td>
<td>78.7 (0.8)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1529</td>
<td>406</td>
<td>59.9 (1.6)</td>
</tr>
</tbody>
</table>

¹All eligible includes all patients that had evaluable immunophenotyping and included both those with and without evaluable cytogenetics.
²13 POG patients could not be classified into NCI risk group due to missing WBC at diagnosis and hence were only included in the overall (Any) analyses.
³The analyses of the CCG data does not include the patients from CCG 1952 and 1961, as they were only included in a limited analysis for TEL-AML1.
⁴Includes all patients who are eligible and have cytogenetic data.
⁵11 of the 5056 POG patients with evaluable cytogenetics could not be classified into NCI risk group due to missing WBC at diagnosis and hence were only included in the overall (Any) analyses.
Table 2 Very High risk ALL criteria (Evaluable cytogenetics; POG 1986 - 1999 and CCG 1988 – 1995)

<table>
<thead>
<tr>
<th>Group</th>
<th>NCI Risk Group</th>
<th>N</th>
<th>5 Year EFS(SE)</th>
<th>8 Year EFS(SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POG</td>
<td>CCG</td>
<td>POG</td>
<td>CCG</td>
</tr>
<tr>
<td>All eligible†</td>
<td>Any</td>
<td>5056</td>
<td>1182</td>
<td>73.0 (0.8)</td>
</tr>
<tr>
<td>Ph+</td>
<td>Any</td>
<td>132</td>
<td>30</td>
<td>27.4 (4.4)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>36</td>
<td>7</td>
<td>52.4(8.8)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>96</td>
<td>23</td>
<td>18.2(5.0)</td>
</tr>
<tr>
<td>&lt;45 CHR</td>
<td>Any</td>
<td>58</td>
<td>14</td>
<td>46.5(7.2)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>27</td>
<td>6</td>
<td>44.4(9.6)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>31</td>
<td>8</td>
<td>48.2(11.0)</td>
</tr>
<tr>
<td>Other *</td>
<td>Any</td>
<td>4866</td>
<td>1138</td>
<td>74.6(0.8)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>3453</td>
<td>763</td>
<td>79.3(0.8)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1402</td>
<td>375</td>
<td>63.1(1.6)</td>
</tr>
</tbody>
</table>

†All eligible includes all patients with evaluable immunophenotyping and evaluable cytogenetics.

‡11 of the 4866 POG patients could not be classified into NCI risk group; due to missing WBC at diagnosis and hence were only included in the overall (Any) analyses.

§Six Ph+ patients had <45 CHR, and are excluded from the <45 CHR group

*Other=those with evaluable cytogenetics that do not have traits listed above it for those risk groups.
Table 3 Evaluation of 11q23 and t(1;19) as an ALL prognostic factor in Children > 12 months of age  

<table>
<thead>
<tr>
<th>Group</th>
<th>NCI Risk Group</th>
<th>N</th>
<th>5 Year EFS(SE)</th>
<th>8 Year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>POG</td>
<td></td>
<td>CCG</td>
</tr>
<tr>
<td>t(4;11)</td>
<td>Any†</td>
<td>44</td>
<td>13</td>
<td>49.9(11.2)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>6</td>
<td>4</td>
<td>50.0(25.0)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>38</td>
<td>9</td>
<td>49.9(12.5)</td>
</tr>
<tr>
<td>Other 11q23</td>
<td>Any</td>
<td>112</td>
<td>18</td>
<td>75.8(4.9)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>71</td>
<td>9</td>
<td>80.2(5.6)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>41</td>
<td>9</td>
<td>68.1(9.3)</td>
</tr>
<tr>
<td>Other *</td>
<td>Any</td>
<td>4710</td>
<td>1107</td>
<td>74.8(0.8)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>3376</td>
<td>750</td>
<td>79.3(0.8)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1323</td>
<td>357</td>
<td>63.3(1.7)</td>
</tr>
<tr>
<td>Balanced t(1;19)</td>
<td>Any#</td>
<td>69</td>
<td>18</td>
<td>68.2(7.3)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>38</td>
<td>9</td>
<td>70.1(9.3)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>31</td>
<td>9</td>
<td>65.8(11.6)</td>
</tr>
<tr>
<td>Unbalanced t(1;19)</td>
<td>Any</td>
<td>194</td>
<td>33</td>
<td>74.1(4.1)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>94</td>
<td>12</td>
<td>80.1(5.1)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>100</td>
<td>21</td>
<td>68.4(6.6)</td>
</tr>
<tr>
<td>Other *</td>
<td>Any</td>
<td>4603</td>
<td>1087</td>
<td>74.7(0.8)</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>3321</td>
<td>742</td>
<td>79.3(0.9)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1271</td>
<td>345</td>
<td>62.6(1.7)</td>
</tr>
</tbody>
</table>

2 11 of the POG patients could not be classified into NCI risk group; due to missing WBC at diagnosis and hence were only included in the overall (Any) analyses.
*Other=those with evaluable cytogenetics that do not have traits listed above it for those risk groups.
† t(4;11) vs. 11q23 vs. Other: Any (POG p< 0.0001, CCG p=0.004); Std risk (POG p=0.039, CCG p=0.002); High risk (POG p=0.009, CCG p=0.091);
# Bal t(1;19) vs. Unbal t(1;19) vs. Other: Any (POG p=0.235, CCG p=0.02); Std risk (POG p=0.0.294, CCG p=0.05); High risk (POG p=0.677 CCG p=0.41).
<table>
<thead>
<tr>
<th>Group</th>
<th>NCI Risk Group</th>
<th>N</th>
<th>5 Year EFS(SE)</th>
<th>8 Year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>POG</td>
<td>CCG</td>
<td>POG</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>High</td>
<td>849</td>
<td>208</td>
<td>54.1(2.2)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>680</td>
<td>198</td>
<td>67.1(2.3)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afr. Amer</td>
<td>High</td>
<td>165</td>
<td>36</td>
<td>53.1(5.0)</td>
</tr>
<tr>
<td>Hisp</td>
<td></td>
<td>225</td>
<td>29</td>
<td>54.3(4.8)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1139</td>
<td>340</td>
<td>61.9(1.8)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15.00</td>
<td>High</td>
<td>1360</td>
<td>343</td>
<td>60.9(1.7)</td>
</tr>
<tr>
<td>&gt;15.00</td>
<td></td>
<td>169</td>
<td>63</td>
<td>51.1(5.4)</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>High</td>
<td>1421</td>
<td>367</td>
<td>61.6(1.6)</td>
</tr>
<tr>
<td>&gt;200</td>
<td></td>
<td>108</td>
<td>39</td>
<td>38.6(6.0)</td>
</tr>
<tr>
<td><strong>CNS status at diagnosis</strong>*</td>
<td></td>
<td>482</td>
<td>1037</td>
<td>75.6(7.9)</td>
</tr>
<tr>
<td>CNS2</td>
<td></td>
<td>326</td>
<td>70</td>
<td>65.0(3.4)</td>
</tr>
<tr>
<td>CNS3</td>
<td></td>
<td>105</td>
<td>21</td>
<td>64.6(5.4)</td>
</tr>
<tr>
<td>CNS1</td>
<td>Std</td>
<td>3193</td>
<td>712</td>
<td>79.9(0.9)</td>
</tr>
<tr>
<td>CNS2</td>
<td></td>
<td>176</td>
<td>38</td>
<td>70.1(4.5)</td>
</tr>
<tr>
<td>CNS3</td>
<td></td>
<td>48</td>
<td>8</td>
<td>71.8(7.6)</td>
</tr>
<tr>
<td>CNS1</td>
<td>High</td>
<td>1181</td>
<td>325</td>
<td>64.0(1.8)</td>
</tr>
<tr>
<td>CNS2</td>
<td></td>
<td>150</td>
<td>32</td>
<td>59.0(5.3)</td>
</tr>
<tr>
<td>CNS3</td>
<td></td>
<td>55</td>
<td>13</td>
<td>58.7(7.5)</td>
</tr>
<tr>
<td><strong>Testicular status at diagnosis</strong>*</td>
<td></td>
<td>2667</td>
<td>618</td>
<td>71.4(1.1)</td>
</tr>
<tr>
<td>Testes-</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testes+²</td>
<td></td>
<td>10</td>
<td>8</td>
<td>90.0(12.7)</td>
</tr>
</tbody>
</table>

* Excludes <45 Chromosomes and Ph+ ALL
1 A total of 4813 POG patients (excluding Ph+ and <45 chromosomes) had known CNS status at diagnosis. Of these, 10 patients (8 CNS1 and 2 CNS3) could not be classified into NCI risk group due to missing WBC at diagnosis, and hence were only included in the overall (Any) analyses.
2 Six boys with testicular disease were known to be NCI standard risk, seven were NCI high risk. Two failed, one per risk group, both in year one.
Table 5. Evaluation of rapidity of response as an ALL prognostic factor\textsuperscript{1} (Evaluable cytogenetics. Excludes <45 Chromosomes and Ph+ ALL)

<table>
<thead>
<tr>
<th>Group</th>
<th>NCI Risk Group</th>
<th>N</th>
<th>5 Year EFS(SE)</th>
<th>8 Year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7 Marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RER (M1/M2)</td>
<td></td>
<td>CCG</td>
<td>713</td>
<td>84.3(1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82.0(8.0)</td>
</tr>
<tr>
<td>SER (M3)</td>
<td></td>
<td>Std</td>
<td>233</td>
<td>75.7(3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74.6(12.5)</td>
</tr>
<tr>
<td>RER (M1/M2)</td>
<td></td>
<td>High</td>
<td>704</td>
<td>76.4(2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74.6(21.7)</td>
</tr>
<tr>
<td>SER (M3)</td>
<td></td>
<td></td>
<td>268</td>
<td>69.4(4.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60.7(38.0)</td>
</tr>
<tr>
<td>Day 14* Marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RER (M1)*</td>
<td></td>
<td>CCG</td>
<td>835</td>
<td>84.4(1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82.4(6.7)</td>
</tr>
<tr>
<td>SER (M2/3)</td>
<td></td>
<td>Std</td>
<td>107</td>
<td>66.6(5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65.4(38.5)</td>
</tr>
<tr>
<td>RER (M1)*</td>
<td></td>
<td>High</td>
<td>819</td>
<td>77.0(2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73.4(21.9)</td>
</tr>
<tr>
<td>SER (M2/3)</td>
<td></td>
<td></td>
<td>113</td>
<td>59.0(7.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59.0(37.8)</td>
</tr>
</tbody>
</table>

This data was obtained from patients treated on CCG 1961 high risk (N=946) and CCG 1952 standard risk (N=1874) protocols only since day 7 and 14 marrow response data were not available on earlier studies. This data is not available for POG studies.

* Day 14 bone marrows were not performed if the day 7 bone marrow was M1. Day 7 M1 marrows were included in the M1 marrows at day 14.


<table>
<thead>
<tr>
<th>Group</th>
<th>NCI Risk Group</th>
<th>N</th>
<th>5 Year EFS(SE)</th>
<th>8 Year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>POG</td>
<td>CCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POG</td>
<td>CCG</td>
</tr>
<tr>
<td>Trisomies 4, 10, and 17</td>
<td>Std</td>
<td>747</td>
<td>89.3(1.4)</td>
<td>91.5(2.8)</td>
</tr>
<tr>
<td>Other *</td>
<td></td>
<td>2706</td>
<td>76.6(1.0)</td>
<td>78.6(1.7)</td>
</tr>
<tr>
<td>TEL/AML1*</td>
<td>Std</td>
<td>115</td>
<td>85.1(10.4)</td>
<td>86.2(4.0)</td>
</tr>
<tr>
<td>Other*</td>
<td></td>
<td>345</td>
<td>77.7(6.8)</td>
<td>80.5(2.3)</td>
</tr>
</tbody>
</table>

*Other=Those with evaluable cytogenetics that do not have traits listed above it for those risk groups. (Hypodiploid and 9-22 excluded) 12 patients with trisomies 4, 10, and 17 had EMD (CNS or testicular) and all but one are in CCR.

* TEL/AML1 status was determined retrospectively, in a subset of the patients on POG studies 9201, 9405, 9605 (using Southern Blot) and the CCG 1952 study.
Figure 1  Algorithm of evaluable patients on CCG and POG studies

All B-Precursor ALL patients treated on CCG or POG protocols

CCG - 4986 patients
POG - 6793 patients

Evaluable patients with immunophenotyping

CCG - 3056 patients
POG - 6793 patients

With both evaluable immunophenotyping and cytogenetics

CCG - 1182 patients
POG - 5056 patients

Early Marrow Response
(Later patients with both evaluable immunophenotyping and cytogenetics)

CCG 1952 (standard risk ALL)
440 evaluable
- 946 with evaluable Day 7 BM
- 942 with evaluable day 14 BM

CCG 1961 (high risk ALL)
972 evaluable
- 972 with evaluable day 7 BM
- 932 with evaluable day 14 BM

TEL-AML1 analysis
(Later patients with both evaluable immunophenotyping and cytogenetics)

CCG 1952
- 440 patients

POG AlinC16 standard risk
- 460 patients
Figure 2a

Age 1.0-9.99 years
WBC < 50,000/ul
B precursor ALL only

Triple trisomies OR TEL-AML1, &
Day 8 or 15 marrow M1, &
Day 29 marrow M1, &
Day 29 MRD < 0.1%, &
No CNS 2/3, or testicular disease

No triple trisomies OR TEL-AML1, &
Day 8 or 15 marrow M1, &
Day 29 marrow M1, &
Day 29 MRD < 0.1%

ANY patient with:
CNS 3 or testicular disease, OR
Day 15 marrow M2/M3, OR
Day 29 MRD ≥ 0.1% - 1%, OR
Identified MLL translocation with a RER, or
Steroid pretreatment (selected cases)

Standard Risk - Low

Standard Risk - Average

Standard Risk - High: Non-Random Assignment to Augmented Therapy
Figure 2b

Age $\geq$ 10 years, and/or
WBC $\geq$ 50,000/ul
B-Precursor ALL only

Day 8 or 15 marrow M1, &
Day 29 marrow M1, &
Day 29 MRD $<$ 0.1%, &
No CNS 3 or testicular disease

High Risk:
Randomized to therapy

Day 15 marrow M2/M3, or
Day 29 MRD $\geq$ 0.1 and $<$ 1%, or
CNS 3 or testicular disease, or
Identified MLL translocation with a RER, or
Steroid pretreatment (selected cases)

High Risk:
Assignment to augmented therapy
Figure 2c

- M2 marrow on Day 29, and/or
- Day 29 MRD ≥ 1%

↓

Extended Induction for NCI SR and HR B-precursor ALL

- Cytogenetic, FISH or molecular evidence of a t(9;22) and/or BCR/ABL fusion, or
- DNA index < 0.81 or < 44 chromosomes or other clear evidence of a hypodiploid clone, or
- Cytogenetic, FISH or molecular evidence of an MLL translocation with a SER, or
- Induction failure defined as M3 bone marrow aspirate on Day 29, regardless of cellularity, or
- M2 Marrow Day 29 and/or Day 29 MRD burden ≥ 1%, with M2/M3 Marrow Day 43 and/or Day 43 MRD burden ≥ 1%

↓

Transfer to Very High Risk Study after Induction
Figure 3a

![Graph showing event-free survival probability over years followed for different risk groups.](graph.png)

- **Low Risk (n=168)**: 4-yr EFS = 0.91 (SE 0.02)
- **Standard Risk (n=529)**: 4-yr EFS = 0.86 (SE 0.02)
- **High Risk (n=768)**: 4-yr EFS = 0.76 (SE 0.02)
- **Very High Risk (n=70)**: 4-yr EFS = 0.46 (SE 0.07)

Event-Free Survival Probability vs. Years Followed
Figure 3b

- Low Risk (n=555)
- Standard Risk (n=1437)
- High Risk (n=912)
- Very High Risk (n=72)

Event-Free Survival Probability

4-yr EFS

Low Risk: 0.92 (SE.01)
Std Risk: 0.82 (SE.01)
High Risk: 0.73 (SE.01)
VHR: 0.29 (SE.05)

Years Followed
Figure legends

Figure 1 ALL Risk Assignment Algorithm
Algorithm for data analysis of POG and CCG data. The figure shows the number of evaluable patients in each of the analyses performed. Because the POG had a central immunophenotyping and molecular laboratory system and the CCG relied on peripheral laboratory results, the attrition of evaluable patients in the POG analysis was much less.

Figure 2 Risk Assignment Algorithms
Each of the algorithms show the criteria for placement of patients in a) standard risk and b) high risk, c) very high risk assignment. Very high-risk assignment occurs independent of initial NCI risk assignment (standard or high risk). Patients who have received less than 48 hours of oral or IV steroids during the week immediately prior to diagnosis are eligible for classification if the results of a CBC, obtained prior to the initiation of steroid therapy (< 72 hours prior to steroids) are available, and the necessary FISH, cytogenetic, and molecular are interpretable. The “pre-steroid” CBC and age of the patient is used to determine NCI-Rome risk classification (SR vs. HR). If the patient has received > 48 hours of oral or IV steroids (and a pre-steroid CBC is available to assign NCI risk group) they are treated as an SER and non-randomly assigned to the augmented regimen. In the absence of a “presteroid” CBC, patients who have received < 48 hours of steroids are assigned to the HR protocol. These patients are eligible for randomization on the HR protocol. As expected, patients with a slow early response will be assigned to the full augmented BFM treatment arm. In the absence of a “presteroid” CBC patients who have received > 48 hours of steroids are treated as an SER on the HR study and assigned to the full augmented arm. Inhalational steroids are not considered as pretreatment. Both SR and HR
patients with identified MLL translocations or CNS 3, or testicular disease, receive augmented SR therapy.

Figure 3. Outcome after classification by the COG risk classification algorithm

a) CCG-1950s/60s B-precursor ALL event-free survival outcome by COG risk classification algorithm. The p-value for the log rank test was <0.0001, Hazard Ratios (with Low Risk being the baseline) was 1.53 for standard risk, 2.73 for high risk and 8.82 for very high risk, b) POG ALinC 16 B-precursor ALL event-free survival outcome by COG Risk Classification Algorithm. (Does not include rapidity of response since those data were not collected for these studies) The p-value for the log-rank test was <0.0001. Hazard Ratios, (with the low risk group being the baseline) was 2.05 for Standard Risk, 3.34 for High Risk, and 15.02 for Very High Risk.
REFERENCES


Risk and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG)


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