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Treatment of higher risk acute lymphoblastic leukemia in young people (CCG-1961), long-term follow-up: a report from the Children's Oncology Group

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Abstract

Children's Cancer Group CCG-1882 improved outcome for 1–21-year old with high risk acute lymphoblastic leukemia and Induction Day 8 marrow blasts 25% (slow early responders, SER) with longer and stronger post induction intensification (PII). This CCG-1961 explored alternative PII strategies. We report 10-year follow-up for patients with rapid early response (RER) and for the first time details our experience for SER patients. A total of 2057 patients were enrolled, and 1299 RER patients were randomized to 1 of 4 PII regimens: standard vs. augmented intensity and standard vs. increased length. At the end of interim maintenance, 447 SER patients were randomized to idarubicin/cyclophosphamide or weekly doxorubicin in the delayed intensification phases. The 10-year EFS for RER were $79.4 \pm 2.4\%$ and $70.9 \pm 2.6\%$ (hazard ratio = 0.65, 95% CI 0.52–0.82, $p < 0.001$) for augmented and standard strength PII; the 10-year OS rates were $87.2 \pm 2.0\%$ and $81.0 \pm 2.2\%$ (hazard ratio = 0.64, 95% CI 0.48–0.86, $p = 0.003$). Outcomes remain similar for standard and longer PII, and for SER patients assigned to idarubicin/cyclophosphamide and weekly doxorubicin. The EFS and OS advantage of augmented PII is sustained at 10 years for RER patients. Longer PII for RER patients and sequential idarubicin/cyclophosphamide for SER patients offered no advantage. CCG-1961 is the platform for subsequent COG studies.

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Introduction

For children and adolescents with acute lymphoblastic leukemia (ALL) initial treatment is assigned by presenting clinical and laboratory features [1, 2]. Initial response to induction therapy, whether determined by Day 8 peripheral blast count [3], Day 8 or 15 marrow blast percentage [4], or end induction minimal residual disease (MRD) by PCR or flow cytometry [5–7] reliably divides patients into subsets with better and worse prognosis. Prior to the availability of MRD, the Children's Cancer Group (CCG) used early marrow response to allocate therapy

Improved post induction intensification (PII) has improved survival for young people with ALL [8–11]. The Berlin Frankfurt Münster (BFM) group introduced Protocol IB (Consolidation) in 1970 [12], almost 50 years ago, and Protocol II (Delayed Intensification, DI) in 1976 [13]. CCG-105, 106, 123, 1881, and 1891 confirmed the value of PII in various patient subsets [8, 14]. On CCG-1882, Nachman et al. [15] found that longer and stronger PII, i.e., “Augmented BFM,” improved outcomes for young people with NCI/Rome high risk features (HR) and Induction Day 8 marrow blasts $\geq 25\%$ (slow early response, SER).

CCG-1961, reported here followed, testing longer versus stronger PII in HR patients, both T- and B-ALL, with a rapid Day 8 marrow response (marrow blasts $<25\%$, rapid early response (RER)) and comparing sequential idarubicin/cyclophosphamide (i/c) versus weekly doxorubicin in DI in SER patients. The 5-year outcomes for RER patients have been reported previously [16].

These studies provide the platforms for subsequent Children's Oncology Group (COG) trials.

Patients and methods

The CCG-1961 enrolled patients September 1996 to May 2002. Patients included those age 10 to 21 years, or age ≥ 1 with presenting WBC count $\geq 50,000/\text{ul}$. Diagnosis was assessed on morphologic, histochemical, and immunophenotypic features of leukemia cells, and reactivity with monoclonal antibodies to lymphoid differentiation antigens associated with B-cell or T-cell lineage as described previously [16]. CNS positivity at diagnosis (CNS-3) and CNS relapse were defined as $\geq 5 \text{ WBC}/\text{mm}^3$ in the CSF with blasts seen on the cytopspin preparation. For patients with a red blood cell contamination, the Steinherz-Bleyer algorithm [17] was used: $\text{CNS-3: CSF WBC}/\text{mm}^3 / \text{CSF RBC}/\text{mm}^3 \times \text{blood WBC}/\text{mm}^3 / \text{blood RBC}/\text{mm}^3$.

Induction therapy consisted of intravenous VCR $1.5 \text{ mg}/\text{m}^2/\text{week}$ and daunorubicin (DNM) $25 \text{ mg}/\text{m}^2/\text{week}$ for 4 weeks; oral prednisone $10 \text{ mg}/\text{m}^2/\text{day}$ for 28 days; native *e. coli* asparaginase $6000 \text{ Units}/\text{m}^2$ intramuscularly thrice weekly for nine doses; intrathecal (IT) cytarabine on day 1 and IT methotrexate (MTX) on days 8 and 29. All patients had a bone marrow aspirate performed on day 8. Bone marrow biopsies were not used in this study for response assessment. Marrow evaluations were not centrally reviewed.

Native asparaginase was used in induction as on past CCG trials to preserve the early marrow response. After induction, one dose of pegaspargase replaced six doses of native asparaginase on the augmented or increased intensity arms.

Because of the high incidence of osteonecrosis on CCG-1882 [18], patients allocated to two DI phases, received dexamethasone 10 mg/m² divide bid, days 1–7 and 15–21, rather than days 1–21.

Patients who were CNS-3 or who were Philadelphia chromosome positive at diagnosis were excluded from any randomization. They were assigned to full augmented BFM therapy with sequential i/c in place of weekly doxorubicin in each of two DI phases. All received 18 Gy cranial radiation starting Day 1 of Augmented Consolidation. CNS-3 patients also received 0.6 Gy spinal irradiation.

Other patients with Day 8 marrow blasts <25% and Day 29 marrow blasts <25% were designated rapid early responders (RER) and randomly allocated to longer or stronger PII and to stronger or standard intensity PII at the end of induction. Regimens are outlined on Table 1. No patient received whole brain irradiation. Longer intensification included two interim maintenance (IM) phases and two DI phases. Augmented intensification included additional vincristine and pegaspargase during periods of myelosuppression and treatment interruption in the consolidation and DI phases and vincristine, escalating-dose intravenous methotrexate, and asparaginase (Capizzi methotrexate) [19] in the IM phases.

SER patients were randomly assigned at the start of the first DI phase to sequential i/c or weekly doxorubicin in each of the two DI phases. Patients on augmented BFM received doxorubicin 25 mg/m² × 3 in each of 2 DI phases (Table 1). Steinherz et al. [20] reported most rapid blast reduction with sequential anthracycline/cyclophosphamide in the Induction phase of the successful New York regimens. In addition, a single course of idarubicin seemed to delay though not prevent relapse in patients with ALL and a first marrow relapse [21].

Therapy lasted two years for girls and three years for boys from Day 1 of the first IM phase.

This protocol was approved by the National Cancer Institute and Institutional Review Boards of the participating institutions. Informed consent was obtained from the patients, their parents, or both as deemed appropriate according to the Department of Health and Human Services guidelines. Analyses performed in this paper were based on data as of December 2013 with 11 years of follow-up after study closure.

Study design and statistical analysis

At the end of induction, RER patients were randomly allocated standard or longer and standard or stronger PII with a 2 × 2 factorial design. SER patients with marrow blasts <25% at the end of IM#1 were randomly allocated to sequential i/c or weekly doxorubicin in each of two DI phases. Balanced block randomization was used to ensure that approximately equal numbers of patients were randomly assigned to each regimen. The study was monitored by an independent Data and Safety Monitoring Committee (DSMC).

The original target enrollment was based on the number of RER patients on study, 1052 randomized patients, which would result in statistical power of ~96% at the final analysis to detect a relative hazard rate 0.626 (i.e., a 37% reduction in the EFS failure rate) and power of ~78.3% to detect a relative hazard rate of 0.715 for either of the main regimen comparisons in the 2×2 factorial design. At the recommendation of the DSMC, in October 2000, the study duration was extended in order to attain the planned randomization accrual for the SER patients. Since response status is not known until day 8 after enrollment on the study, the RER accrual was also extended to coincide with achieving the SER accrual target.

The monitoring boundary for the RER comparison of increased intensity versus standard intensity was crossed in February 2003 when the p -value reached $p = 0.0198$ (the boundary value at the time was $p < 0.0229$), and at that time the study results for the RER patients were released. The initial results for the RER patients was published in 2008 [21]. Long-term outcomes for the RER patients together with outcomes for the SER cohort are presented in this report.

The main analytic endpoints were event-free survival (EFS) and overall survival (OS). EFS and OS rates at 5 or 10 years from date of enrollment were reported for all eligible patients enrolled on the study. For the comparison of EFS and OS between SER vs. RER patients, EFS and OS times were calculated from day 29 of Induction. For the randomized group comparisons, EFS and OS times were calculated from the date of randomization (day 29 of induction for RER patients and day 57 of IM#1 for SER patients). EFS was defined as time to first event (relapse, second malignancy (SMN), or death) or last follow-up for patients who were event-free, and OS was defined as time to death or last follow-up for those who were alive. Comparisons of randomized treatment regimens were performed by intent-to-treat.

Survival estimates were calculated by the Kaplan–Meier (KM) method with the standard error (SE) after Peto method [22, 23]. Five-year and 10-year survival rates (with associated SE) are presented here. Survival curves were compared using the log rank test. Given that we report long-term outcomes, we also analyzed our data and compared plateaus of EFS and OS curves using parametric non-mixture cure models [24]. Cumulative incidence rates of relapse, SMN, and remission death were estimated accounting for competing risks. Comparisons of cumulative incidence curves between groups were made using competing risks regression analyses [25]. Patient and disease characteristics were compared between groups with chi-squared tests for homogeneity of proportions. Comparison of the proportion of grade 3+ toxicities on the SER treatment arms was based on logistic regression models. Since there were four treatment phases after SER randomization, each patient would contribute toxicity data for one or more treatment phases, and this feature was treated as a random effect in the logistic regression analysis.

All reported p -values are two-sided. Statistical analyses were performed using STATA 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: Sta-taCorp LLC).

Results

All patients

A total of 2078 patients were enrolled (Consort diagram, Fig. 1). Twenty-one patients were found to be ineligible for the study (six patients because of improper consents, two patients started chemotherapy prior to signing the consent, eight patients were found to have malignancies other than ALL, two patients received steroids longer than 48 h prior to diagnosis, two standard risk patients had been mistakenly enrolled on 1961, and one patient did not have an evaluable bone marrow result). The remaining 2057 patients were eligible. Median duration of follow-up was 9.6 years. The 5- and 10-year EFS ($\pm$ SE) were $71.8 \pm 1.1\%$ and $68.5 \pm 1.5\%$ from entry. The 5- and 10-year OS ($\pm$ SE) were $81.2 \pm 0.9\%$ and $77.1 \pm 1.3\%$.

The 5- and 10-year EFS rates for B lineage patients ($n = 1101$) were $70.4 \pm 1.5\%$ and $67.3 \pm 2.1\%$, respectively; for T-ALL patients ($n = 413$), $73.5 \pm 2.3\%$ and $71.4 \pm 3.1\%$, respectively; and for mixed lineage patients ($n = 151$), $71.9 \pm 3.9\%$ and $67.4 \pm 5.8\%$, respectively. The 5- and 10-year OS rates for B lineage patients were $81.7 \pm 1.2\%$ and $76.6 \pm 1.9\%$, respectively; for T-ALL patients, $79.9 \pm 2.1\%$ and $78.1 \pm 2.9\%$, respectively; and for mixed lineage patients, $79.5 \pm 3.5\%$ and $74.7 \pm 5.4\%$, respectively.

RER and SER patients

Twenty-seven eligible patients died in induction (27/ 2057, 1.3%); 24 had Day 29 marrow blasts $\geq 25\%$ (24/2057, 1.2%). Thirty-six had inevaluable Day 8 or Day 29 marrow aspirates.

A total of 1970 patients had evaluable Day 8 and Day 29 marrow aspirates and achieved Day 29 marrow blasts $<25\%$, including CNS-3 and Philadelphia chromosome positive patients. The 5- and 10-year EFS were $74.1 \pm 1.1\%$ and $70.6 \pm 1.5\%$, starting with the end of Induction. The 5- and 10-year OS were $83.4 \pm 0.9\%$ and $79.3 \pm 1.3\%$.

Among the 1970 patients, 71.4% were RER ($n = 1406$) and 28.6% were SER ($n = 564$, Fig. 1). The numbers differ slightly from the 2008 report [16]. RER and SER patients had significant differences in some presenting features (Table 2). For example, SER patients were more likely to have high initial white cell counts and/or T-lineage.

By lineage, the 5-year EFS for RER and SER B-lineage patients ($n = 1058$) was $74.1 \pm 1.7\%$ and $68.3 \pm 2.9\%$; for T-ALL patients ($n = 393$), $77.2 \pm 2.7\%$ and $74.8 \pm 4.0\%$; and for the small number of mixed lineage patients ($n = 144$), $75.1 \pm 4.2\%$ and $70.6 \pm 8.8\%$. Hazard ratios reached conventional statistical significance for the large B-lineage subset (Fig. 2) but not for the smaller T-ALL and mixed lineage subsets.

The 10-year EFS and OS for RER patients was $72.7 \pm 1.8\%$ and $81.7 \pm 1.5\%$; for SER patients, $65.3 \pm 2.8\%$ and $73.2 \pm 2.6\%$. SER patients had significantly worse EFS ($p = 0.003$) and OS ($p < 0.001$) than RER patients (Fig. 3a, b). OS was about 9 percentage points higher than EFS for RER patients at 10 years and 8 points higher for SER patients. For both SER and RER patients, only about 25% of patients could be rescued after relapse.

The variety of failure events in the RER and SER patients was generally similar. SER patients had a higher marrow relapse rate ($p < 0.001$) and a slightly higher remission death rate ($p = 0.047$) than RER patients (Fig. 2c, Table 3). Of interest, non-CNS3 T-cell SER patients received 18 Gy whole brain irradiation and had a lower incidence of CNS relapse (2/132) than non-CNS3 T-cell RER patients who received no whole brain irradiation (22/261) ($p = 0.018$).

Randomized RER patients

Excluding patients who were not randomized (parental choice or physician's decision), CNS-3, or Philadelphia chromosome, a total of 1299 eligible randomized RER patients were assigned to one of four treatment regimens, namely standard length and intensity (standard BFM, 1 DI: $n = 322$), greater length but standard intensity (standard BFM, 2 DI: $n = 327$), standard length but stronger intensity (augmented BFM, 1 DI: $n = 327$) and greater length and greater intensity (augmented BFM, 2 DI: $n = 323$).

The 5-year outcomes of randomized RER patients were reported previously [16]. Here we report the 10-year outcomes. At 10-year, the EFS rates were $79.4 \pm 2.4\%$ and $70.9 \pm 2.6\%$ (hazard ratio = 0.65, 95% confidence interval or CI 0.52–0.82, $p < 0.001$) with augmented and standard strength PII; the 10-year OS rates were $87.2 \pm 2.0\%$ and $81.0 \pm 2.2\%$ (hazard ratio = 0.64, 95% CI 0.48–0.86, $p = 0.003$). Outcomes remain similar for standard and longer duration PII. For EFS and OS rates of each of the four treatment regimens, please see Fig. 4.

Outcomes also appear improved for adolescent and young adult patients (AYA), aged 16–21 years. For 164 randomized AYA RER patients, the 10-year EFS rates were $74.4 \pm 8.2\%$ and $67.6 \pm 8.4\%$ for augmented and standard strength PII (hazard ratio = 0.65, 95% CI 0.36–1.19, $p = 0.16$). This difference was not statistically significant with the comparatively small sample size of the AYA patients, but the hazard ratio is similar to the entire RER cohort.

The results reported here confirm our previous conclusion, i.e., stronger intensification significantly improved patients' EFS ($p < 0.001$) and OS ($p = 0.003$), while longer intensification offers no advantage (EFS: $p = 0.66$; OS: $p = 0.54$). Augmented therapy offers a persistent EFS advantage of ~10 percentage points at 5 years and 9 percentage points at 10 years. Augmented therapy offers an OS advantage of ~5 percentage points at 5 years and 6 percentage points at 10 years. The long-term EFS and OS advantage of stronger intensification was further supported by parametric cure model tests that focused on testing the differences in the plateaus of the EFS or OS curves, the p -values being very similar to the ones reported above.

Randomized SER patients

A total of 447 SER patients were randomly allocated prior to starting DI, 224 to the weekly doxorubicin arm and 223 to the i/c arm. Patients with erroneous randomization, Philadelphia chromosome, CNS-3, or marrow blasts $\geq 25\%$ at the end of IM#1 were excluded. Other than minor, likely inconsequential, differences in platelet count, no important differences were observed in presenting characteristics (Table 2).

We found no difference in EFS or OS of SER patients randomized to weekly doxorubicin or sequential i/c in each DI phase ($p = 0.22$ for EFS and $p = 0.16$ for OS (Fig. 5). Doxorubicin re-induction resulted in a 5-year EFS and OS of $76.3 \pm 3.1\%$ and $83.4 \pm 2.7\%$ while the 5-year EFS and OS with i/c were $71.3 \pm 3.2\%$ and $80.3 \pm 2.9\%$ respectively. The types of failure events were similar in either arm.

Toxicity

The grade 3+ toxicities observed in the SER weekly doxorubicin and i/c arms were generally similar, except that patients on the sequential i/c arm had a somewhat higher infection rate ($p = 0.013$). The rates of grade 3 or 4 infections for the i/c arm vs. the doxorubicin arm were 18.1% (39 patients; 29 bacterial; 12 fungal) vs. 7.9% (17 patients; 6 bacterial; 6 fungal) during DI 1, and were 14.1% (28 patients; 14 bacterial; 6 fungal) vs. 9.2% (19 patients; 11 bacterial; 8 fungal) during DI 2. A patient may have had more than one documented infection in the phase. One remission death was reported on the doxorubicin arm and five on the i/c arm. Patients on the two arms had similar average hospital days and ICU days.

Discussion

Early marrow response successfully divides patients into subsets with better or worse prognosis [4]. Over the past 20 years centralized flow cytometry has trumped local microscopy [5]. Flow cytometry in expert hands better predicts outcome in discordant cases [26].

Borowitz et al. [5] reported that adjustment for end induction MRD in multivariate analyses eroded any prognostic significance for early marrow response by microscopy. End induction and end consolidation MRD have replaced early marrow response by microscopy though earlier marrow examination by flow cytometry retains prognostic significance [27, 28]. The transition from central to local MRD determination will entail some challenge [29].

Augmented therapy on CCG-1961 differed from CCG1882 in several regards. SER patients on CCG-1882 received 54 doses of native asparaginase. CCG1961 employed native asparaginase in induction, in order to “preserve early response rates” followed by pegaspargase thereafter and encountered the same problem with frequent clinical allergy [16]. Subsequent COG studies have used pegaspargase in induction and thereafter, except in the case of clinical allergy. SER patients on CCG1882 received 21-day continuous courses of dexamethasone in each of 2 DI phases [15]. CCG1961 introduced split course dexamethasone to mitigate osteonecrosis. This was carried forward on AALL0232 and halved the incidence of osteonecrosis in adolescents and young adults [30].

The 5-year results for the RER subset have been previously reported. The EFS and OS advantage of stronger intensification is sustained at 10 years. The MRC (UK) 2003 study also found an advantage for augmented therapy [31].

This study found no advantage for a longer intensification with a second DI phase in the RER subset. This was confirmed for lower risk patients on the CCG1991 [14] and the MRC

(UK) ALL 2003 studies [32]. The value of longer intensification has not been tested in SER patients. However, longer intensification had no advantage in any subset of CCG 1961 RER patients.

At 5 years, EFS for SER patients was $70.2 \pm 2.0\%$. On the predecessor study CCG1882, the 5-year EFS was $75.0 \pm 3.8\%$ [15]. Patient populations are not identical and these results are not dissimilar.

After completion of IM#1, SER patients were randomized to receive either 2 DI courses with either doxorubicin weekly $\times 3$ or sequential i/c. Published results suggested that idarubicin may be a more active anthracycline against leukemia than doxorubicin [33] and be able to cross the blood-brain barrier [34]. The Memorial Sloan Kettering Cancer Center New York II found most rapid cytorreduction with daunomycin by 48-h infusion, followed by cyclophosphamide on day 3 [20]. Lacking published data for idarubicin by 48 h continuous infusion, we administered it as two 4-h infusions on days 1 and 2 with cyclophosphamide on day 3 on this study (Table 1). In this study, outcomes were similar with both approaches. We found more common grade 3–4 infections but no increased GI toxicity with idarubicin.

Subsequent COG studies, some now completed, build on these results. AALL0232 further improved EFS for B-lineage patients by replacing prednisone with dexamethasone for younger patients and replacing the Capizzi methotrexate with 5 g/m^2 methotrexate in the IM phase [35]. In T-ALL, AALL0434 showed an EFS advantage for adding nelarabine [36] and curiously found Capizzi methotrexate, which includes additional asparaginase, superior to 5 g/m^2 methotrexate [37].

An excess of CNS relapses was seen among unirradiated T-ALL RER patients compared to the irradiated T-ALL SER patients and led to the inclusion of whole brain irradiation for about 90% of patients on AALL0434 [37]. The 5-year cumulative incidence rates of isolated CNS relapse on AALL0434 were 0.4% (0–1.0%) for Capizzi and 3.0% (1.4–4.6%) for 5 g/m^2 methotrexate ($p = 0.001$). Other strategies may improve CNS control with no irradiation [38–40].

This is a rare study that has patient follow-up data for more than 11 years. In the past most relapses occurred within 3 years of diagnosis [41, 42]. More recently, two-thirds of relapses occur after 3 years [43]. Treatment interventions may delay but not prevent relapse, e.g., Borowitz et al. found a transient early advantage for HR patients with greater Day 29 MRD between 0.1 and 1% who received two DI phases compared to putatively better prognosis patients with lesser Day 29 MRD between 0.01 and 0.1% who received a single DI phase. The EFS curves cross at 3 years and by 5 years; patients with greater Day 29 MRD have a worse prognosis as expected [5]. In the clinic, early differences may decrease with longer follow-up, e.g., Capizzi versus 5 g/m^2 methotrexate on AALL0232 [35]. The proportional hazards assumption is frequently violated.

The commonly employed log rank test, which compares the survival distributions of two or more groups, is most powerful when the proportional hazards assumption holds. However, when the proportional hazards assumption fails, the log rank test may not be optimal. If early differences in EFS or OS diminish with longer follow-up, it may be misleading. In a

disease like ALL where cure is possible, the EFS or OS plateau may be of greater clinical interest than shorter term effects. Interventions that delay but not prevent relapse may still add to morbidity and block potentially more useful interventions. Assessment of treatment effects requires adequately long follow-up and appropriate statistical tests. In this age of small molecules with early, transient effects and immune therapies with delayed, persistent effects alternatives to the log rank test need be considered [44].

In summary, 2057 patients with NCI/Rome high risk ALL had a 5- and 10-year EFS ($\pm$ SE) were $71.8 \pm 1.1\%$ and $68.5 \pm 1.5\%$. The 5- and 10- year OS ($\pm$ SE) were $81.2 \pm 0.9\%$ and $77.1 \pm 1.3\%$. The previously reported advantage for augmented intensification is sustained at 10 years and confirmed using a parametric cure model comparing plateaus. Prolonged intensification had no advantage over standard length PII. Sequential idarubicin/cyclophosphamide in DI had no advantage over the usual weekly doxorubicin. This study provides the platform for subsequent COG studies, AALL0232, AALL1131, AALL0434, and AALL1231.

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Key points

- In all, 2057 high risk ALL patients had a 5- and 10-year EFS of $71.8 \pm 1.1\%$ and $68.5 \pm 1.5\%$. The 10-year EFS rate for rapid early responders was 79.4%.
- EFS for slow responders was 70.2% and 65.3% at 5 and 10 years. Advantage of augmented intensification seen at 5 years, was sustained at 10 years.

Fig. 1.
CCG 1961 consort diagram

Fig. 2.

EFS for RER and SER patients, by lymphoblast lineage. **A** EFS of B-cell, RER vs. SER, **B** EFS of SER B-cell vs. T-cell vs. mixed lineage

Fig. 3.

Comparison of EFS (A) and OS (B) between SER vs. RER patients, and cumulative incidence of failure events (C) for SER vs. RER patients

Fig. 4.
EFS and OS for RER patients by randomized regimen. **A** RER EFS by regimen, **B** RER OS by regimen

Fig. 5. EFS and OS for SER patients by randomized regimen. **A** EFS of SER Doxo vs. Ida, **B** OS of SER Doxo vs. Ida

Table 1

Treatment phases of the CCG-1961 study

Phase	Rapid early responders (RER)				Slow early responders (SER)	
	Arm A	Arm B	Arm C	Arm D	Doxo ^a	IDA-C ^d
1. Induction (IND)	35 day IND	35 day IND	35 day IND	35 day IND	35 day IND	35 day IND
2. Consolidation (CONS)	35 day CONS	35 day CONS	63 day CONS	63 day CONS	63 day CONS	63 day CONS
3. Interim maintenance (IM) I	56 day IM	56 day IM	56 day IM (CAP)	56 day IM (CAP)	56 day IM (CAP)	56 day IM (CAP)
4. Delayed intensification (DI) I	49 day DI	49 day DI	56 day DI	56 day DI ^b	56 day DI ^b	56 day DI/ IDA-C
5. Interim maintenance II		56 day IM		56 day IM	56 day IM	56 day IM
6. Delayed intensification II		49 day DI ^b		56 day DI ^b	56 day DI ^b	56 day DI ^b /IDA-C
7. Maintenance cycles (M) ^c	84 day M	84 day M	84 day M	84 day M	84 day M	84 day M

^aDelayed intensification/reconsolidation I & II for SER patients treated with doxorubicin or sequential idarubicin/ cyclophosphamide^bIndicates slight differences in DI course from the treatment given in arms A and C^cRepeat for 2 years of total therapy for girls & and 3 years for boys from day 0 of IM I**Doxorubicin (DI)**Day 1,8,15 Vincristine 1.5 mg/m² IVDay 1,8,15 Doxorubicin 25 mg/m² IVDay 1 to 7, 15 to 21 Dexamethasone 10 mg/m²/day PODay 3, 42 PEG Asparaginase 2500 U/m² IMDay 28 Cyclophosphamide 1000 mg/m² IVDay 29 to 43 Thioguanine 60 mg/m²/d x 14 PODay 29 to 32, 36 to 39 Cytosine Arabinoside 75 mg/m² IV or SQDay 42 to 49 Vincristine 1.5 mg/m² IV

Day 1 & 28 Methotrexate by age 8, 10 or 12 mg IT

Sequential Idarubicin/cyclophosphamide (IDA-C)Day 1,8,15 Vincristine 1.5 mg/m² IVDay 1, 2 Idarubicin 10 mg/m² IV

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Day 1 to 7, 15 to 21 Dexamethasone 10 mg/m²/day PO
Day 3, 42 PEG Asparaginase 2500 U/m² IM
Day 3 Cyclophosphamide 1000 mg/m² IV
Day 29 to 43 Thioguanine 60 mg/m²/d x 14 PO
Day 29 to 32, 36 to 39 Cytosine Arabinoside 75mg/m² IV or SQ
Day 42 to 49 Vincristine 1.5 mg/m² IV
Day 1 & 28 Methotrexate by age 8, 10 or 12 mg IT

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Table 2

Characteristics of all SER vs RER patients, and of randomized SER patients

Variables	SER vs. RER		Randomized SER Patients	
	SER (n = 564)	RER (n = 1406)	<i>p</i> -value ^b	Doxo (n = 224) i/c (n = 223)
<i>Age (yrs)</i>			0.29	
1–9	227 (40.2%)	515 (36.6%)		89 (39.7%) 89 (39.9%)
10–15	266 (47.2%)	714 (50.8%)		108 (48.2%) 107 (48.0%)
16+	71 (12.6%)	177 (12.6%)		27 (12.1%) 27 (12.1%)
<i>Sex</i>			0.24	
Male	348 (61.7%)	827 (58.8%)		139 (62.1%) 134 (60.1%)
Female	216 (38.3%)	579 (41.2%)		85 (37.9%) 89 (39.9%)
<i>Race</i>			0.047	
Caucasian	358 (63.7%)	962 (69.4%)		139 (62.1%) 149 (66.8%)
Black	41 (7.3%)	80 (5.8%)		18 (8.0%) 16 (7.2%)
Other ^a	163 (29.0%)	344 (24.8%)		67 (29.9%) 58 (26.0%)
Unknown	2	20		
<i>WBC x 10³/mm³</i>			<0.001	
<50	228 (40.5%)	709 (50.5%)		93 (41.5%) 95 (42.8%)
50–199	251 (44.6%)	545 (38.8%)		100 (44.6%) 94 (42.3%)
200+	84 (14.9%)	150 (10.7%)		31 (13.8%) 33 (14.9%)
Missing	1	2		1
<i>Hemoglobin/dl</i>			0.077	
1–7.9	262 (48.8%)	611 (45.0%)		105 (49.1%) 105 (50.0%)
8–10.9	174 (32.4%)	427 (31.5%)		77 (36.0%) 63 (30.0%)
11+	101 (18.8%)	319 (23.5%)		32 (15.0%) 42 (20.0%)
Missing	27	49		10 13
<i>Platelets x 10³/mm³</i>			0.29	
1–49	281 (50.0%)	746 (53.4%)		106 (47.3%) 117 (52.9%)
50–149	203 (36.1%)	454 (32.5%)		75 (33.5%) 82 (37.1%)
150+	78 (13.9%)	196 (14.0%)		43 (19.2%) 22 (10.0%)
Missing	2	10		2

Variables	SER vs. RER		Randomized SER Patients	
	SER (<i>n</i> = 564)	RER (<i>n</i> = 1406)	<i>p</i> -value ^{<i>b</i>}	Doxo (<i>n</i> = 224) i/c (<i>n</i> = 223)
<i>Immunophenotype</i>				
B lineage	277 (63.2%)	781 (67.5%)	0.002	100 (58.8%) 113 (64.2%)
T lineage	132 (30.1%)	261 (22.6%)		57 (33.5%) 51 (29.0%)
Mixed	29 (6.6%)	115 (9.9%)		13 (7.6%) 12 (6.8%)
Unknown	126	249		54 47
<i>Mediastinal mass</i>				
Absent	495 (87.9%)	1179 (84.2%)	0.036	196 (87.5%) 191 (86.0%)
Present	68 (12.1%)	221 (15.8%)		28 (12.5%) 31 (14.0%)
Missing	1	6		1
<i>Hepatomegaly</i>				
Normal	159 (44.3%)	443 (47.4%)	0.32	60 (42.3%) 60 (42.9%)
Enlarged	164 (45.7%)	419 (44.9%)		63 (44.4%) 71 (50.7%)
Below Umbilicus	36 (10.0%)	72 (7.7%)		19 (13.4%) 9 (6.4%)
Missing	205	472		82 83
<i>Splenomegaly</i>				
Normal	237 (42.1%)	584 (41.7%)	0.67	100 (44.6%) 88 (39.6%)
Enlarged	255 (45.3%)	658 (47.0%)		94 (42.0%) 108 (48.6%)
Below Umbilicus	71 (12.6%)	159 (11.3%)		30 (13.4%) 26 (11.7%)
Missing	1	5		1
<i>Lymphadenopathy</i>				
Normal	241 (42.9%)	657 (46.8%)	0.086	95 (42.6%) 90 (40.5%)
Enlarged	258 (45.9%)	628 (44.8%)		101 (45.3%) 107 (48.2%)
Below Umbilicus	63 (11.2%)	118 (8.4%)		27 (12.1%) 25 (11.3%)
Missing	2	3		1 1

^aOther includes Hispanic, Oriental, Hawaiian, Native American, Indian Subcontinent, Filipino, and other

^b*P*-values: Pearson's chi-square, excluding missing

Table 3

Number of patients with each type of failure events

Type of events	RER				SER			
	RER (n = 1406)	RER-B cell (n = 781)	RER-T cell (n = 261)	Mixed (n = 115)	SER (n = 564)	SER-B cell (n = 277)	SER-T cell (n = 132)	Mixed (n = 29)
Event free	1037	572	196	80	376	174	97	21
Bone marrow relapse	212	127	26	22	125	66	27	6
Isolated CNS relapse	73	39	22	5	17	11	2	0
Testicular relapse	14	10	2	0	7	5	0	0
Second malignancy	19	8	4	2	9	5	2	1
Death in CR	43	21	10	5	28	16	3	1
Other events	8	4	1	1	2	0	1	0
Total events	369 (26.2%)	209 (26.8%)	65 (24.9%)	35 (30.4%)	188 (33.3%)	103 (37.2%)	35 (26.5%)	8 (27.6%)