Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children’s Oncology Group Study AALL0031

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AUTHOR CONTRIBUTIONS
Kirk R Schultz designed the research, performed the research, analyzed the data and wrote the paper. Andrew Carroll performed the research, analyzed the data and wrote the paper. Nyla A Heerema performed the research, analyzed the data and wrote the paper. W Paul Bowman designed the research, performed the research, analyzed the data and wrote the paper. Alexander Aledo designed the research, performed the research and wrote the paper. William B Slayton designed the research, performed the research and wrote the paper. Harland Sather designed the research, analyzed the data and wrote the paper. Meenakshi Devidas designed the research, analyzed the data and wrote the paper. Hao W Zheng analyzed the data. Stella M Davies designed the research and wrote the paper. Paul S Gaynon designed the research and wrote the paper. Michael Trigg designed the research and wrote the paper. Robert Rutledge designed the research and wrote the paper. Dean Jorstad designed the research and wrote the paper. Naomi Winick performed the research and wrote the paper. Michael J Borowitz performed the research, analyzed the data and wrote the paper. Stephen P Hunger designed the research, performed the research and wrote the paper. William L Carroll designed the research, performed the research and wrote the paper. Bruce Camitta designed the research, performed the research and wrote the paper.

CONFLICT OF INTEREST
The authors declare no conflict of interest.
Abstract

We previously reported preliminary findings that post induction imatinib mesylate (340 mg/m²/day), in combination with intensive chemotherapy, resulted in outcomes similar to blood and marrow transplant (BMT) for pediatric patients with Philadelphia chromosome-positive (Ph +) acute lymphoblastic leukemia (ALL). We now report 5-year outcomes of imatinib plus intensive chemotherapy in 91 children (1–21 years) with and without allogeneic BMT (N = 91). We explore the impacts of additional chromosomal abnormalities and minimal residual disease (MRD) by flow cytometry on outcomes. The 5-year disease-free survival was similar for Cohort 5 patients, treated with chemotherapy plus imatinib (70% ± 12%, n = 28), sibling donor BMT patients (65% ± 11%, n = 21) and unrelated donor BMT patients (59 ± 15%; P = 0.60, n = 13). Patients with additional cytogenetic abnormalities had worse outcomes (P = 0.05). End induction (pre-imatinib) MRD was not prognostic for Cohort 5 or allogeneic BMT patients, although limited by small numbers. The re-induction rate following relapse was similar to other higher-risk ALL groups. Longer-term follow-up confirms our initial observation of substantially good outcomes for children and adolescents with Ph + ALL treated with imatinib plus intensive chemotherapy with no advantage for allogeneic BMT.

Keywords
imatinib mesylate; Philadelphia chromosome; acute lymphoblastic leukemia; toxicity; event-free survival; blood and marrow transplantation

INTRODUCTION

Although the t(9;22)/Philadelphia chromosome (Ph +) is present in only 3–5% of children with acute lymphoblastic leukemia (ALL), fewer than 40% of Ph + ALL patients are cured with intensive chemotherapy regimens, and allogeneic blood and marrow transplant (BMT) was considered to be the best therapy for a curative outcome before the advent of tyrosine kinase inhibitor (TKI) therapy.1-5 Unfortunately, allogeneic BMT has significant long-term mortality and morbidity.
The Children’s Oncology Group (COG) AALL0031 study included both Ph + and Ph – very high risk (VHR) pediatric ALL patients, that is, those with an expected 5-year event-free survival (EFS) less than 45% with conventional chemotherapy. Patients received 4 weeks of standard induction chemotherapy. Those identified as VHR were entered on AALL0031 after appropriate informed consent. The novel AALL0031 chemotherapy regimen was derived from previous Pediatric Oncology Group chemotherapy strategies and included rigorous post-induction intensification followed by continuation therapy. Imatinib (340 mg/m²/day for 21 days) was included for Ph + ALL patients during an increasing number of treatment blocks in the first four patient cohorts (44 pts), followed by continuous dosing during intensive chemotherapy and intermittent during maintenance therapy in Cohort 5 (50 patients). Patients who had an HLA-identical family donor underwent BMT after the first two cycles of AALL0031 protocol therapy. Another group was removed from protocol for unrelated donor BMT. Their outcomes were collected. Preliminary results of Ph + ALL patients treated on Cohort 5 demonstrated that the addition of imatinib resulted in a significant improvement of the 3-year EFS rate compared with historical controls treated without imatinib. Neither matched sibling donor nor unrelated donor allogeneic BMT offered a benefit compared with Cohort 5 imatinib with chemotherapy.

Additional follow-up was required to determine whether our promising early results would be sustained over time and whether allogeneic BMT gives a superior outcome with longer follow-up. The current analysis provides the long-term follow-up for this population with a median follow-up time of 5.2 years from study entry. We compare the outcome of Cohort 5 therapy with allogeneic BMT. We also examined the presence of additional cytogenetic abnormalities and minimal residual disease (MRD) as possible prognostic factors that might be used for future treatment allocation. A Japanese study of adults with Ph + ALL reported an adverse prognostic significance for associated chromosomal abnormalities, even in patients treated with imatinib-combined chemotherapy and BMT. The overall 2-year EFS in that study was 48.5±5.7%, and the 50 patients with secondary chromosomal abnormalities had a 35—40% lower EFS than those with t(9;22) only (P = 0.003). Last, we retrospectively surveyed centers to determine whether patients who relapse after imatinib and chemotherapy treatment can be induced into a second remission, potentially allowing salvage with allogeneic BMT in 2nd complete remission (CR2).

PATIENTS AND METHODS

Patients

COG AALL0031 enrolled patients aged 1–21 years with very high risk ALL from 10/14/2002 until 10/20/2006. The therapy is described in a previous publication. A large subset of patients enrolled on therapy had the Philadelphia chromosome [t(9;22)(q34;q11.2)] detected by conventional or molecular cytogenetics or BCR-ABL1 fusion transcript identified by reverse transcription polymerase chain reaction. Included were Ph + ALL patients with induction failure defined as either > 25% blasts (M3 marrow status) by histology at the end of 4 weeks of induction therapy or an M2 marrow status (5–25% blasts by histology) or MRD ≥1% by flow cytometry at the end of induction, followed by an M2 (or M3), marrow status or MRD ≥1% after receiving two additional weeks of induction.
therapy (defined as M2/M2 induction failures). No imatinib or other TKI was administered before enrollment in COG AALL0031.

**Treatment schema**

The therapy received by these patients has been previously described\(^8\) in detail. In brief, all patients enrolled in the study received a minimum of two consolidation chemotherapy blocks. Patients with an HLA-matched related donor then proceeded to BMT. Total duration of chemotherapy with imatinib was approximately 27 months for those not receiving BMT. Prior approval was obtained from the National Cancer Institute, and the Institutional Review Boards of the COG member institutions. Informed consent of the patient/parent and assent of patient were obtained in accordance with Federal guidelines.

**Imatinib therapy**

From Cohort 1 to 5, patients received an increasing exposure to imatinib (340 mg/m\(^2\)), as detailed in our previous publication.\(^8\) In brief, more days of imatinib 340 mg/m\(^2\)/day were introduced in a stepwise manner. Toxicity was assessed for each cohort before progression to the next cohort. Cohort 1 had seven patients after published data demonstrated acceptable imatinib toxicity with high-dose methotrexate.\(^10\) Cohorts 2–4 had 12 patients each. Cohort 5 was expanded to accrue a total of 50 patients in order to provide a more precise estimate of outcome. With a cohort size of 12, a 90% confidence interval provides an estimate± ~24%, that is, the true EFS result could be 24-percentage points higher or lower than the observed estimate. Increasing the size of the final cohort to 50 reduced the confidence interval to ±12%. The total imatinib exposure of 340 mg/kg/day escalated from minimal exposure in Cohort 1 to a maximum exposure in Cohort 5 for a median of 708 days (maximum of 867 days). Imatinib started after conclusion of induction therapy. For all patients receiving BMT on protocol, imatinib was given between weeks 16 and 24 after BMT when the ANC was ≥750 and the platelet count was ≥75,000 for a total of 24 weeks. Patients were given imatinib at 230 mg/m\(^2\)/day and increased after 28 days to 340 mg/m\(^2\)/day if no grade 3 or grade 4 toxicity was observed.

**MRD assessment**

MRD was assessed by multiparameter flow cytometry at study entry (after completing conventional induction therapy) and after the first and second blocks of consolidation therapy at a single central reference lab, as described.\(^11,12\) Samples were available from 119 of 133 (89%) patients at study entry.

**Statistical analysis**

The primary outcomes were EFS for noninduction failure patients and disease-free survival (DFS) for induction failure patients enrolled in the study. EFS was calculated as the time from study entry to first event or last contact, where an event was defined as relapse at any site, secondary malignancy or death. DFS time was calculated in a similar manner with time measured from the end of consolidation block 2. Patients who did not achieve remission by the end of consolidation block 2 or those who did not complete consolidation block 2 were removed from DFS analyses. AALL0031 study data were frozen on 30 September 2011 for
these analyses. Patients who did not fail were censored as of the date of last contact. Survival estimates were computed using the Kaplan–Meier method, and standard errors of the estimates were determined according to Peto and Peto. The log-rank test was used for comparison of survival curves between groups.

RESULTS

Patient characteristics

Ninety-five Ph + ALL patients were enrolled. Two patients were ineligible because of an invalid consent (Ph + Cohort 3), and one patient was retrospectively found to have chronic myeloid leukemia in lymphoid blast crisis. Among the 92 eligible Ph + patients in Cohorts 1–5, nine had induction failure (M3 at the end of induction) before entering AALL0031, with one additional M2/M2 induction failure excluded from analysis. One patient enrolled in the study was inevaluable (Ph + Cohort 1). Median age at diagnosis for the Ph + patients was 10 years (range 1.3–21 years). Other characteristics of this population have been previously described.

The Ph + induction failure patients (N = 10) were excluded from all analyses except for a comparison of outcomes vs Ph + noninduction failure patients.

Long-term outcome of intensive chemotherapy and imatinib (Cohort 5) compared with HLA-identical sibling donor BMT

In our previous report, we found that patients treated with intensive imatinib in combination with intensive chemotherapy for approximately 2.5 years (Cohort 5) had a 3-year EFS of 88±11%. Median follow-up time for the current analysis is 5.2 years, with a minimum of 0.5 years and a maximum of 7.9 years. Ph + patients (N = 91) had a 5-year overall survival of 70±6%. The 5-year EFS for all cohorts (induction failure patients excluded) was 58±6% (N = 81). There was no difference in 5-year DFS (Figure 1a) for patients in Cohort 5 treated with chemotherapy plus imatinib (70±12%) compared with those who received BMT in all cohorts either from a related donor BMT (65±11%) or unrelated donor BMT (59±15%; P = 0.60). To evaluate the impact of pre-BMT intensive TKI therapy on BMT outcome, we limited our analysis only to those who were in Cohort 5 in the analysis. Figure 1b gives similar DFS comparisons as in Figure 1a except that the BMT patients included were those in Cohort 5 only. EFS analyses performed in the previous report were also replicated with the longer follow-up. Excluding induction failures, 5-year EFS for chemotherapy patients in Cohort 5 was 71±12%, compared with 64±12% for related donor BMT patients and 63±16% for unrelated donor BMT patients (P = 0.77). As documented in the previous report, 5-year DFS of induction failure patients (69±27%) was not significantly different from that of noninduction failure patients (58±6%, P = 0.69).

Evaluation of the predictive ability of MRD for outcomes in Ph + ALL

We evaluated a number of potential prognostic factors and their impact on treatment outcome. We evaluated the impact of MRD at study entry (end of induction). Cohorts 3 and 4 were combined, and 5-year EFS for those with MRD ≤0.01% at study entry (prior to any imatinib exposure) was 100% (n = 3) compared with 38±15% (N = 14) for those with MRD >0.01% (P = 0.08) (Figure 2a). Similar to our previous report, MRD levels at the end of induction did not predict outcome in Cohort 5 (Figure 2b). Patients receiving continuous...
imatinib had a strong trend toward an improved EFS in MRD-negative patients with a 5-year EFS of 88±10 vs 65±11% (\(P = 0.17\)) for those with MRD ≤0.01% (\(N = 16\)) compared with >0.01% (\(N = 23\)). Analysis for significance was limited by small patient numbers. High MRD burden later in therapy has usually predicted a poorer outcome more accurately,\(^1\) and a low MRD burden before BMT has also been predictive of an improved outcome.\(^5\) To perform a comparison on the predictive ability of MRD in Cohort 5 chemotherapy versus BMT, we evaluated the predictive ability of MRD after consolidation block 2 (three cycles of chemotherapy in total) for Cohort 5 patients and BMT patients from all cohorts.\(^1\)-\(^5\) We found that the MRD burden at the end of consolidation block 2 did not predict outcome for the Cohort 5 chemotherapy group (Figure 2c), with a 5-year EFS of 85±14% for MRD ≤0.01% (\(N = 13\)) versus 100% for MRD >0.01% (\(N = 2\); \(P = 0.57\)). MRD levels at the end of consolidation 2 also did not predict outcome in those patients receiving either an unrelated or related donor BMT from all cohorts with 77±13% 5-year EFS for MRD ≤0.01% (\(N = 14\)) compared with 40±22% for MRD >0.01% (\(N = 5\); \(P = 0.18\)).

**Evaluation of the prognostic impact of the presence of additional cytogenetic abnormalities in Ph + ALL**

Secondary chromosomal aberrations are frequently identified at initial diagnosis in pediatric and adult patients with Ph + ALL, and several studies have shown that the presence of additional cytogenetic abnormalities is a major negative prognostic factor.\(^9\) We evaluated the prognostic impact of secondary chromosomal abnormalities (in addition to the Ph +) present at initial diagnosis (Figure 3). Satisfactory cytogenetic results were available for 69 (76%) of 91 eligible patients with Ph + ALL enrolled in AALL0031. Secondary cytogenetic aberrations were present in 44 (64%) patients, the most frequent being +der(22) (\(N = 17\)), X50 chromosomes (\(N = 14\)), −7/del(7p) (\(N = 10\)), abnormal (9p) (\(N = 9\)) and + 8 (\(N = 6\)). The overall 5-year EFS was 67±7% for patients in cohorts 4/5, including those with unevaluated cytogenetics (\(N = 54\)). For those with known cytogenetic data (\(N = 42\)), 5-year EFS for patients with Ph + alone (\(N = 14\)) was 86±10% versus 51±11% for those with Ph + and secondary abnormalities (\(N = 28\)) (\(P = 0.05\)).

**Rates of second complete remission for Ph + ALL patients following relapse**

To determine the potential ability of BMT to salvage patients who relapse following treatment with intensive chemotherapy plus imatinib as given in AALL0031, we conducted a retrospective survey of the centers that had patients who relapsed after chemotherapy plus imatinib treatment on AALL0031 (cohorts 1–5). A second complete remission was attained after relapse on AALL0031 overall in 67% (20/30) of patients. The remission rate was similar for patients that had minimal imatinib exposure before relapse on Cohort 1 with 5/6 (83%) and Cohort 2 (3/6) (50%) and for those that relapsed after more extensive imatinib exposure in Cohorts 3–5 (12/18; 67%). This CR2 was similar to that of patients treated on COG AALL01P2 for high-risk relapses 67%±5.9% (\(N = 63\)) in Ph-negative ALL.\(^16\) Of the patients attaining a remission, 85% remained in remission for ≥3 months (17/20). Of the patients who remained in remission for ≥3 months, 65% (11/17) underwent BMT in CR2.

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DISCUSSION

This study confirms that children and adolescents with Ph + ALL treated with intensive chemotherapy plus intensive imatinib have an excellent outcome that appears to stabilize to about 70–75% long-term outcomes for these patients, although the patient numbers are relatively small. There was no suggestion of an advantage to allogeneic BMT in CR1. The COG has now completed enrollment in a phase II single-arm trial (AALL0622) of the same chemotherapy used in AALL0031 plus the second-generation TKI dasatinib in children and adolescents with Ph + ALL, and the European EsPhALL study has recently been amended to include continuous dosing of imatinib with chemotherapy. The results of the EsPhALL study conducted between January 2004 and December 2009 before amendment showed a benefit in an astreated analysis with a 4-year DFS of 75.2% for good-risk patients receiving imatinib compared with 55.9% for those who did not ($P = 0.06$). Thus, even intermittent imatinib conveyed a survival advantage for good-risk Ph + ALL.

Results of the AALL0622 and the amended EsPhALL studies will provide additional data about outcome for pediatric Ph + ALL following treatment with continuous TKI treatment combined with an intensive chemotherapy backbone. It is uncertain whether or not the long-term toxicities of AALL0031 might be similar to allogeneic BMT (excluding chronic graft-versus-host disease). Patients on Cohort 5 chemotherapy received cumulative doses of cyclophosphamide 11 gm/m$^2$, nine courses of high doses (5 gm/m$^2$/dose) of methotrexate, 36 mg/m$^2$ cytarabine, 9 gm/m$^2$ ifosfamide and 3.5 gm/m$^2$ etoposide. These exposures may result in high male infertility rates, increased risk of central nervous system toxicities and an increased risk of secondary malignancies. As the intensification of imatinib from Cohort 1 to Cohort 5 appears to be the primary factor for the improved outcome in Cohort 5, an intensified TKI regimen (such as second- or third-generation TKIs) with a reduced-intensity chemotherapy background could potentially make such an approach more applicable to adults, and it results in reduced long-term toxicities in children and adolescents.

Previously, the presence of a low MRD burden measured early in therapy or immediately before BMT has been highly predictive of subsequent treatment outcomes in Ph + ALL and other high-risk ALL subtypes. Interestingly, we found that MRD did not predict outcome for patients treated with chemotherapy plus imatinib in Cohorts 3 and 4 or Cohort 5. Previously, we had shown that end of induction MRD burden was highly predictive of outcome for Cohorts 3 and 4 that had less intensive imatinib treatment, but this predictive value has now decreased with longer follow-up. For patients in Cohort 5 treated with intensive imatinib therapy, MRD burden either after induction or after the first 3 cycles of chemotherapy was not predictive of outcome, suggesting that TKIs may minimize the predictive value of MRD. Although the level of MRD before BMT did trend toward a poorer prognosis for patients with a high MRD, it was not significant. It is important to emphasize that all of these analyses are limited by small patient numbers; thus, it will be important to further explore the predictive value of MRD in other trials of chemotherapy plus TKI for Ph + ALL.

In this study, the lower 5-year EFS seen in patients with Ph + ALL with secondary chromosomal abnormalities was marginally significantly different from that for children.
with Ph + alone, possibly reflecting small patient numbers. The lower 5-year EFS for Ph + ALL with secondary chromosomal abnormalities in those treated on AALL0031 appeared to be very similar to that seen in the previous adult trial (~35% lower). 9

One of the issues regarding utilization of chemotherapy and TKI preferentially over allogeneic BMT is the question of whether patients can be salvaged if a relapse occurs. The retrospective survey of the centers in this study that had patients relapse after AALL0031 chemotherapy and TKI from all cohorts demonstrated that the reinduction rate was similar to other high-risk Ph-negative ALL patients treated on contemporaneous COG ALL trials. Thus, patients with Ph + ALL who were treated with chemotherapy plus TKI following relapse had a similar likelihood of attaining CR2 and being able to undergo allogeneic BMT to that of children and adolescents with Ph-negative ALL that relapsed.

Future trials based on the results of COG AALL0031 trial are underway. An international trial evaluating continuous dosing dasatinib, a second-generation TKI with a broader spectrum of activity, in combination with a less intensive chemotherapy back bone is accumulating patients by the COG, primarily in North America, and EsPhALL centers in Italy and the United Kingdom. This study will evaluate whether an intensified TKI regimen with less intensive chemotherapy can give an equivalent outcome with lower toxicity. This may have a major impact on young adults with Ph + ALL who have a lower tolerance of intensified chemotherapy as given in the AALL0031 protocol. Moreover, we hope to minimize the late effects anticipated with the AALL0031 protocol with male infertility and neurotoxicity.

The long-term findings of this study support the conclusion that intensive chemotherapy and prolonged continuous dosing imatinib can replace allogeneic BMT as the preferred approach for children and adolescents with Ph + ALL. Whether this can be extended into the adult populations remains to be evaluated.

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REFERENCES


Figure 1.
Comparison of disease-free survival (DFS) (Patients not in remission by the end of consolidation block 2 and those who did not complete consolidation block 2 were excluded.) for (a) Cohort 5 chemotherapy only vs ALL patients receiving a related BMT vs unrelated BMT. (b) Comparison of disease-free survival (DFS) for cohort 5 chemotherapy only versus cohort 5-treated related and unrelated BMT.
Figure 2.
Impact of MRD on chemotherapy outcomes (a) at study entry MRD on cohort 3/4-treated patients; (b) at study entry MRD on cohort 5-treated patients and (c) end of consolidation 2 MRD in cohort 5 chemotherapy-treated patients; (d) impact of MRD at end of consolidation 2 on BMT outcomes.
Figure 3.
Impact of additional cytogenetic abnormalities on chemotherapy outcomes in (a) cohort 3/4 and (b) cohort 5-treated patients.