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ORIGINAL REPORT

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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Improved Early Event-Free Survival With Imatinib in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Children's Oncology Group Study

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See accompanying editorial on page 5121 and articles on pages 5168 and 5189

ABSTRACT

Purpose
Imatinib mesylate is a targeted agent that may be used against Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), one of the highest risk pediatric ALL groups.

Patients and Methods
We evaluated whether imatinib (340 mg/m^2/d) with an intensive chemotherapy regimen improved outcome in children ages 1 to 21 years with Ph+ ALL (N = 92) and compared toxicities to Ph− ALL patients (N = 65) given the same chemotherapy without imatinib. Exposure to imatinib was increased progressively in five patient cohorts that received imatinib from 42 (cohort 1; n = 7) to 280 continuous days (cohort 5; n = 50) before maintenance therapy. Patients with human leukocyte antigen (HLA) –identical sibling donors underwent blood and marrow transplantation (BMT) with imatinib given for 6 months following BMT.

Results
Continuous imatinib exposure improved outcome in cohort 5 patients with a 3-year event-free survival (EFS) of 80% ± 11% (95% CI, 64% to 90%), more than twice historical controls (35% ± 4%; $P < .0001$). Three-year EFS was similar for patients in cohort 5 treated with chemotherapy plus imatinib (88% ± 11%; 95% CI, 66% to 96%) or sibling donor BMT (57% ± 22%; 95% CI, 30.4% to 76.1%). There were no significant toxicities associated with adding imatinib to intensive chemotherapy. The higher imatinib dosing in cohort 5 appears to improve survival by having an impact on the outcome of children with a higher burden of minimal residual disease after induction.

Conclusion
Imatinib plus intensive chemotherapy improved 3-year EFS in children and adolescents with Ph+ ALL, with no appreciable increase in toxicity. BMT plus imatinib offered no advantage over BMT alone. Additional follow-up is required to determine the impact of this treatment on long-term EFS and determine whether chemotherapy plus imatinib can replace BMT.

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INTRODUCTION

The risk-adjusted acute lymphoblastic leukemia (ALL) trials conducted by the Children's Oncology Group (COG) and others have resulted in great improvements in the survival of children and adolescents with ALL, but specific patient subsets continue to have poor survival.[1] While the positive t(9;22)/Philadelphia chromosome (Ph+) is present in only 3% to 5% of children with ALL, fewer than 40% of Ph+ ALL patients are cured with intensive chemotherapy regimens.[2-5]

Building on evidence that the BCR-ABL oncoprotein resulting from the 9;22 translocation has kinase activity, investigators developed the selective tyrosine kinase inhibitor imatinib mesylate.[6-8] Trials in adults have shown it to be highly active in Ph+ chronic-phase and blastic chronic myelogenous leukemia. Imatinib monotherapy produces a high response rate in Ph+ ALL, but the responses are transient with recurrence in months.[8-11] Daily oral imatinib (260-570 mg/m^2/d) is well tolerated in children and adolescents with leukemia.[12] Common adverse events (AEs) from administration of imatinib

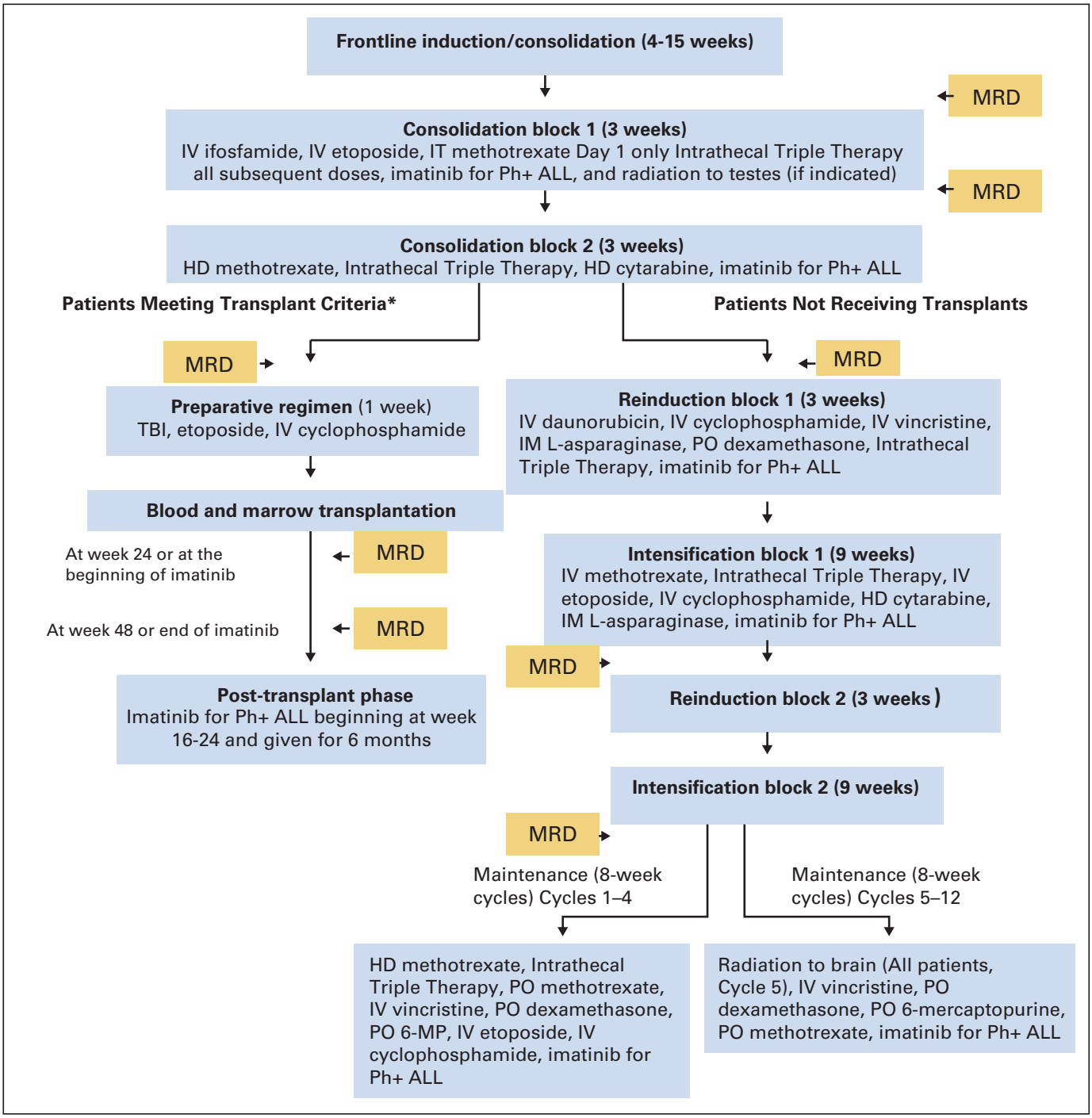

Fig 1. Treatment schema for Children's Oncology Group (COG) protocol AALL0031. At enrollment onto AALL0031, patients had completed 4 to 6 weeks of three-drug or four-drug induction therapy consistent with a front-line pediatric cooperative group (Children's Cancer Group [CCG] or Pediatric Oncology Group [POG]) regimen. MRD, minimal residual disease; IV, intravenous; IT, intrathecal; PH+, Philadelphia chromosome–positive; ALL, acute lymphoblastic leukemia; HD, high dose; TBI, total body irradiation; IM, intramuscular; PO, oral.

in both adults and children include edema/weight gain and toxicity to marrow, liver, gut, and skin. These have been tolerable and usually reverse with dose adjustment.[6,13] Imatinib has been used with intensive hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone therapy followed by blood and marrow transplantation (BMT) in adults,[14] although its efficacy and tolerability given with multiagent chemotherapy in children is not known. Imatinib may also improve the outcome after allogeneic BMT for Ph+ ALL.[15]

The COG AALL0031 study included both Ph+ and Ph− very high-risk (VHR) pediatric ALL patients identified as those with an expected 5-year event-free survival (EFS) of less than 45% with conventional chemotherapy. The chemotherapy regimen was based on previous strategies[16-18] in which patients first received 4 weeks of

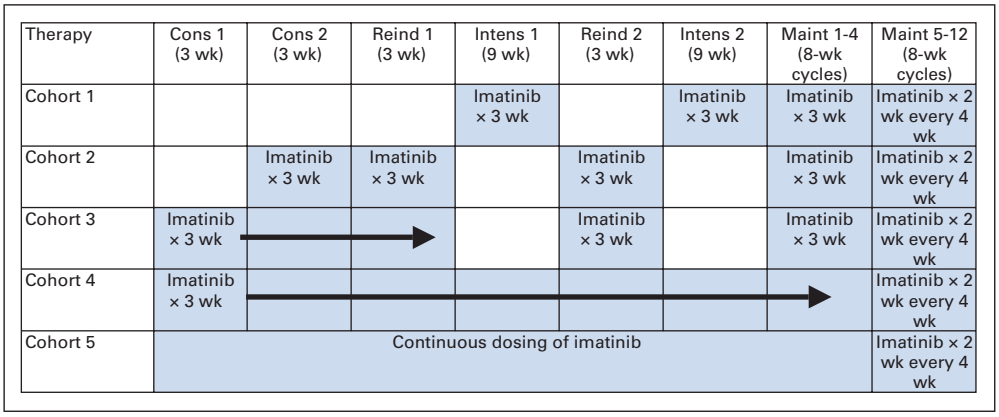

Fig 2. Integration of imatinib into successive blocks of therapy. Imatinib was given at 340 mg/m^2/d (blue blocks) for 21 days (cohorts 1 to 4). Maintenance Blocks 1 through 4 consisted of 3-week blocks and Maintenance Blocks 5 through 12 consisted of 2-week blocks every 4 weeks. In cohort 5, dosing was continuous except for 2 weeks every 4 weeks during Maintenance Blocks 5 through 12. All boxes shaded blue received imatinib during that cycle of therapy. Cons, Consolidation Block; Reind, Reinduction Block; Intens, Intensification Block; Maint, Maintenance Block.

standard induction chemotherapy and were entered onto AALL0031, which included an intensive consolidation phase followed by a continuation regimen (Fig 1). Imatinib (340 mg/m^2/d for 21 days) was included for Ph+ ALL patients during an increasing number of treatment blocks (Fig 2 and Appendix, online only) in the first four patient cohorts (44 patients), followed by continuous dosing in the final patient cohort (50 patients). In maintenance cycles 5 through 12, imatinib was administered intermittently on a 2-week-on/2-week-off schedule. Patients who had a human leukocyte antigen (HLA) –identical family donor underwent BMT after the first two cycles of AALL0031 protocol therapy. Sixty-six Ph− VHR ALL patients enrolled in AALL0031 received the identical chemotherapy without imatinib, allowing for an evaluation of imatinib toxicity.

Early results from AALL0031 demonstrate that addition of imatinib was tolerable and improved 3-year EFS compared with that in historical controls. Matched sibling donor allogeneic BMT does not appear to offer a benefit to early survival.

PATIENTS AND METHODS

Patients

COG AALL0031 enrolled patients ages 1 to 21 years with VHR ALL from October 14, 2002, until October 20, 2006. Because of the delays associated with identification of the VHR markers (Philadelphia chromosome, hypodiploidy, and induction failure), eligible patients were enrolled on protocol with histologically proven ALL after completion of 4 weeks of induction therapy. Induction therapy was limited to a combination of vincristine, asparaginase, prednisone or dexamethasone with or without daunomycin, prednisone, or dexamethasone, and asparaginase with or without daunomycin. VHR features included (1) Philadelphia chromosome t(9;22)(q34;q11.2) detected by conventional or molecular cytogenetics or BCR-ABL fusion transcript identified by reverse transcription polymerase chain reaction; (2) hypodiploidy defined as fewer than 44 chromosomes or DNA index less than 0.8; (3) any rearrangement of the *MLL* gene in conjunction with a slow early response, defined as ≥ 5% marrow blasts at day 15 and/or ≥ 0.1% minimal residual disease (MRD) at the end of induction as detected by multiparameter flow cytometry;[19,20] and (4) induction failure. The latter was defined as more than 25% blasts (M3 marrow status) by histology at the end of 4 weeks of induction therapy, as M2 marrow status (5% to 25% blasts by histology), or as an 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 was administered before enrollment onto COG AALL0031. All patients who were not Ph+ ALL served as the control group in the evaluation of imatinib for additional toxicities on the chemotherapy backbone.

Treatment Schema

All patients enrolled onto the study received a minimum of two consolidation chemotherapy blocks (Fig 1). Patients with an HLA-matched related donor entered the BMT arm following these blocks. Total duration of chemotherapy for those not receiving BMT was approximately 27 months. Prior approval was obtained from the National Cancer Institute (NCI) and the institutional review boards of the COG member institutions. Informed consent of the patient and/or parent and assent of patient were obtained in accordance with federal guidelines.

Imatinib Therapy

For patients with Ph+ ALL, imatinib 340 mg/m^2/d was introduced into the chemotherapy regimen in a stepwise fashion, with toxicity assessed for each cohort before progression to the next cohort as shown in Figure 2. Each cohort had 12 subjects except for cohort 1 (n = 7), which was discontinued early on the basis of published data demonstrating acceptable imatinib toxicity with high-dose methotrexate.[10] Cohort 5 was expanded to accrue a total of 50 patients to provide a more precise estimate of outcome. With the original cohort size of 12, a 90% CI provides a half-width of approximately 24%; that is, the true EFS result could be 24% higher or lower, depending on the observed estimate. Increasing the size of the final cohort reduced the half-width of the CI to 12% to provide reasonable precision. The total imatinib exposure (before maintenance) was 42 days in cohort 1, 63 days in cohort 2 (n = 17), 84 days in cohort 3, 126 days in cohort 4 (n = 22), and 280 days in cohort 5 (n = 44). All groups received an additional 336 days of imatinib exposure in maintenance cycles 1 through 12 (Fig 2). For all patients receiving BMT on protocol, imatinib was started between week 16 and week 24 after BMT when the absolute neutrophil count was ≥ 750 and the platelet count was ≥ 75,000 given for a total of 24 weeks. Dosing started at 230 mg/m^2/d and increased after 28 days to 340 mg/m^2/d if no grade 3 or 4 toxicity was observed.

Toxicity Assessment

Data on AEs and clinically significant abnormal laboratory findings were collected using National Cancer Institute Common Terminology Criteria (CTC) version 2.0. Standard AE reporting was supplemented with NCI's AdEERs (Adverse Event Expedited Reporting System) reports and MedWatch reports (for reporting AEs with commercial agents to the US Food and Drug Administration and NCI). Inclusion of the Ph− patients treated with the identical chemotherapy without imatinib allowed for direct comparison of patients treated with the same chemotherapy backbone with or without imatinib.

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.[21] Samples were available from 119 (89%) of 133 patients at study entry.

Statistical Analysis

The primary outcome was EFS, calculated as the time from entry onto study to first event or last contact, where an event was defined as induction failure, relapse at any site, secondary malignancy, or death. AALL0031 study data were frozen on October 31, 2008, for these analyses. Patients who did not fail were censored as of the date of last contact. Estimates of EFS were computed using the Kaplan-Meier method,[22] and standard errors of the estimates were determined according to Peto and Peto.[23] The log-rank test was used for comparison of survival curves between groups. MRD rates and toxicity rates were compared between groups by using the χ^2 test and Fisher's exact test. Two-sample *t* tests were used to compare course durations between groups. Analyses used a historical control data set of Ph+ patients in remission that included patients enrolled onto the ALinC 14 (Pediatric Oncology Group POG 8602), ALinC 15 (POG 9005 and 9006), and ALinC 16 (POG 9201, 9405, 9406, and 9605) protocols for B-precursor ALL between January 1986 and November 1999. Although related and unrelated BMT patients were part of the historical data set, the percentage of BMT patients compared with the percentage of patients who received chemotherapy is unknown. Induction failures were excluded from the historical controls. The outcome of patients treated on a Children's Cancer Group (CCG) protocol (CCG 1921) with a related-donor BMT for Ph+ ALL was used as a historical control for related-donor BMT.[24] The group did not differ with respect to patient characteristics (age, gender, WBC) from the patients who received a related-donor BMT in this study.

RESULTS

Patient Characteristics

One hundred sixty patients were enrolled. Two patients were ineligible because of an invalid consent (Ph+, cohort 3). The 158 eligible patients included 93 Ph+ patients, 41 with hypodiploidy (< 44 chromosomes), 22 Ph− induction failures, and two with an *MLL* rearrangement and a slow early response. Among the 93 Ph+ patients in cohorts 1 through 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 onto the study was not evaluable (Ph+, cohort 1). Median age at diagnosis for the Ph+ patients was 10 years (range, 1.3 to 21 years). Of the 92 evaluable Ph+ ALL patients, 59 (64%) were male and 69 (75%) were white. Median WBC count at initial diagnosis was 27,000/μL (range, 1,800 to 638,000/μL). The demographic summary was similar to Ph+ ALL patients treated on earlier COG trials. The Ph+ induction failure patients (n = 10) were excluded from all analyses except for comparing their outcomes with those of Ph+ non–induction failure patients. There was concern that AALL0031 accrual might be affected by the fact that unrelated-donor BMT was not allowed on this study. To evaluate this concern, we examined protocol entry among the 34 Ph+ ALL patients initially enrolled on the COG AALL0232 study for high-risk ALL, all of whom were evaluated for the Ph chromosome and recommended to enter AALL0031 protocol if positive. Although patients were not required to be enrolled on frontline COG trials, 24 (71%) of the 34 Ph+ patients initially enrolled on the frontline AALL0232 trial were enrolled on AALL0031. This strongly suggests that for the majority of patients, the prohibition of unrelated-donor BMT was not a factor in deciding whether to enroll on AALL0031.

Impact of Imatinib With Intensive Chemotherapy on Early EFS

The 3-year EFS of patients in cohort 5 receiving continuous imatinib was 80.5% ± 11.2% (95% CI, 64.5% to 89.8%), including those assigned to a sibling BMT. This is significantly higher than historical controls, after excluding induction failures from previous POG studies (N = 120; 3-year EFS, 35.0% ± 4.4%; $P < .0001$; Fig 3) and other published data including 267 children with Ph+ ALL (2-year EFS, 40.9%; 95% CI, 35.5% to 46.3%).[5]

Toxicities Associated With Imatinib and Intensive Chemotherapy

A direct comparison of toxicities for each block of therapy was performed for those VHR ALL patients who did (Ph+) and did not receive imatinib. Those who did not receive imatinib included hypodiploid patients, induction failures, and Ph+ patients who did not receive imatinib in an earlier block. A midstudy analysis demonstrated a higher incidence of ALT elevation during maintenance cycle 2 (7 of 42 *v* 1 of 27), cycle 5 (10 of 25 *v* 5 of 18), and cycle 6 (9 of 24 *v* 4 of 13) for those receiving imatinib. After identification of hypertransaminasemia, therapy was amended such that the duration of imatinib was shortened from 21 days to 14 days in each 4-week maintenance cycle. A postamendment analysis found that the altered imatinib dosing in maintenance cycles 5 through 12 resulted in a decrease in ALT grade ≥ 3 toxicity from 54% (17 of 31) before the amendment to 28% (11 of 40) after the amendment ($P = .01$).

In most phases of therapy, grade ≥ 3 toxicities for Ph+ patients and non-Ph+ patients had about the same frequency. The few significant differences included infection with grade 3/4 neutropenia during Reinduction 2 (19.6% [10 of 51] in the imatinib-treated group *v* 2.2% [1 of 43] in the group that did not receive imatinib; $P = .01$) and lower total WBC ($P = .02$) and hypokalemia in the imatinib group in Consolidation 2 ($P = .04$).

As an aggregate marker for imatinib toxicity, the duration of each of the first four blocks of therapy were compared between the Ph+ group and the non-Ph+ patients. There were no significant differences in Consolidation 2 or Reinduction 1. There were significantly longer delays with imatinib in consolidation 1 (mean ± standard deviation, 23.7 ± 3.3 days *v* 22.3 ± 3.5 days; $P = .01$) and in Reinduction 1 (31.9 ± 10.4 days *v* 27.7 ± 8.5 days; $P = .03$). There were no significant post-BMT imatinib toxicities.

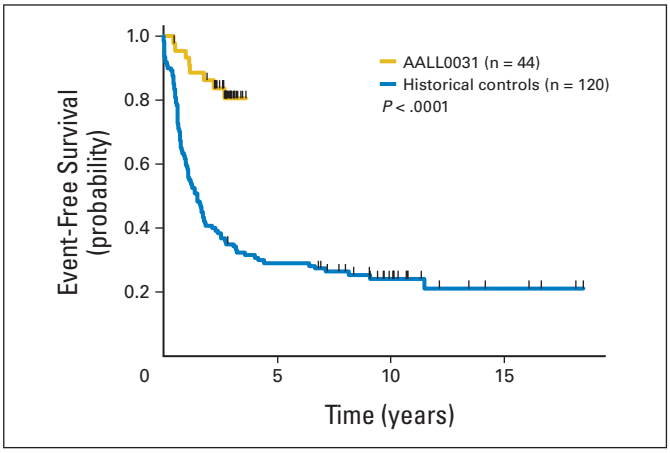

Fig 3. Early event-free survival in Philadelphia chromosome–positive acute lymphoblastic leukemia patients treated with imatinib. Treated patients in cohort 5 (n = 44) were compared with patients previously treated on Pediatric Oncology Group (POG) protocols ALinC 14, 15, and 16 from January 1986 through November 1999 (N = 120).

Impact of Imatinib Mesylate With HLA-Identical Sibling Donor BMT on EFS

Twenty-one patients had matched sibling transplants (8 of 39 in cohorts 1-4 and 13 of 44 in cohort 5). The related-donor BMT group treated with 6 months of imatinib post-BMT had a 3-year EFS (56.6% ± 21.5%) similar to that of a comparable historical (no imatinib) BMT group from CCG 1921[24] (3-year EFS, 66.7% ± 15.7%; n = 9; $P = .80$). In violation of protocol therapy, 11 (13%) of 82 Ph+ patients were removed from AALL0031 by treating institutions for off-protocol alternative (unrelated and mismatched) donor BMT. Outcome analysis of patients (n = 31) enrolled in cohort 5 chemotherapy (including six patients receiving alternative-donor BMT) showed an 86.8% ± 10.0% 3-year EFS, which is similar to results obtained after removal of the six off-protocol BMT patients (3-year EFS, 87.7% ± 10.9%). There was no significant difference in 3-year EFS between patients (n = 25) treated with cohort 5 chemotherapy (87.7% ± 10.9%; 95% CI, 66.4% to 95.8%), patients (n = 21) receiving BMT from a sibling donor (56.6% ± 21.5%; 95% CI, 30.4% to 76.1%), and patients (n = 11) receiving BMT from an alternative donor (71.6% ± 19.0%; 95% CI, 35.0% to 89.9%; $P = .14$; Fig 4). These three groups were similar with respect to age at diagnosis, sex, and race. Comparison of the nine Ph+ induction failures (> 25 blasts at end of induction; Fig 5) at study entry versus the other 82 Ph+ patients, including all treatment cohorts, showed no significant difference in 3-year EFS (50% ± 35.4% *v* 66.2% ± 7.4%; $P = .27$) although the patient numbers were small.

Evaluation of Risk Factors That Have an Impact on the Therapeutic Outcome in Ph+ ALL

We evaluated a number of factors and their impact on therapeutic outcome in Ph+ ALL. Evaluation of NCI high-risk versus standard-risk patients showed no significant difference in the 3-year EFS (58.6% ± 8.4% *v* 82.8% ± 11.5%; $P = .09$). Even when age and WBC were analyzed separately in the NCI high-risk group, there was no significant difference ($P = .64$) among patients who were ≥ 10 years old with WBC ≥ 50,000 (3-year EFS, 38.7% ± 14.5%), those who were less than 10 years old with WBC ≥ 50,000 (58.2% ± 14.2%), and those who were ≥ 10 years old with WBC less than 50,000 (66.3% ± 12.2%). When cohorts 3 and 4 were combined, those with an MRD ≤ 0.01% at study entry (end induction, before any imatinib exposure) had a better 3-year EFS than those with an MRD of more than 0.01% (100% [n = 5] *v* 38.6% ± 15.1% [n = 14]; $P = .02$) (Fig 6A). In contrast, end induction MRD levels did not predict outcome in cohort 5 patients (Fig 6B) receiving continuous imatinib with a 3-year EFS of 88.2% ± 17.5% versus 75.9% ± 14.1% ($P = .41$) for those with MRD ≤ 0.01% (n = 18) compared with those having MRD of more than 0.01% (n = 26).

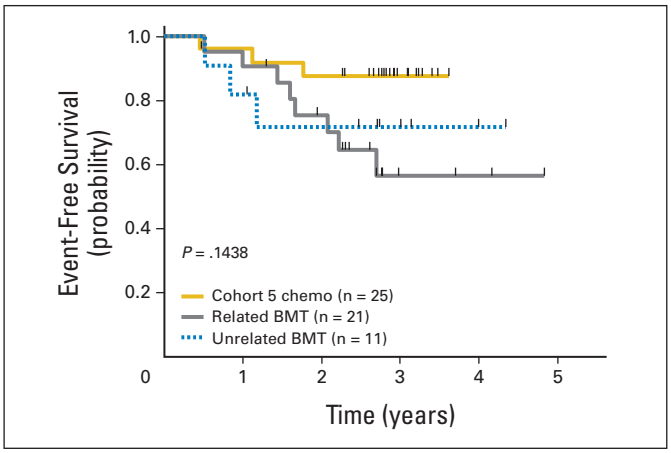

Fig 4. Comparison of event-free survival (EFS) for Cohort 5 chemotherapy only versus related-donor bone marrow transplantation (BMT) versus unrelated-donor BMT. Cohort 5 patients were compared with human leukocyte antigen (HLA) –identical sibling BMT (8 of 39 in cohorts 1-4; 13 of 44 in cohort 5) and 11 of the total 83 patients removed from protocol for an alternative-donor BMT. Patients treated on protocol were given imatinib 340 mg/m^2/d for 6 months starting 4 to 6 months after BMT.

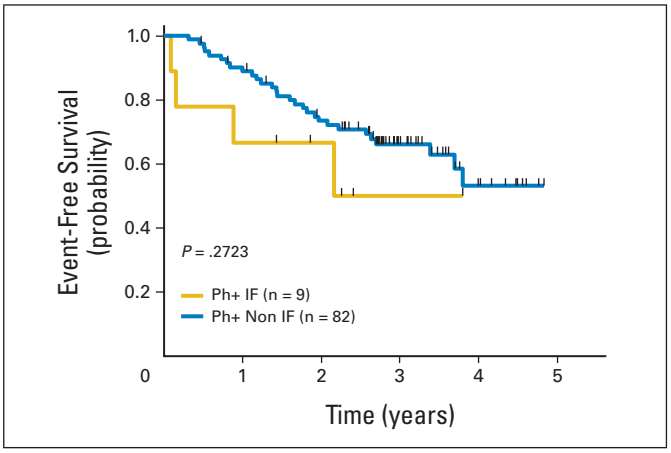

Fig 5. Comparison of event-free survival for Philadelphia chromosome–positive (Ph+) induction failures (IFs) at study entry versus Ph+ non–induction failures (Non IF). Ph+ patients who were classified as IFs (n = 9; all cohorts) at end of induction (> 25 blasts) were compared with Ph+ patients treated on all cohorts (N = 82).

DISCUSSION

While the overall outcome for children with ALL has improved, the cure rate for specific VHR subgroups including those with Ph+ ALL have been disappointing. Identification of the underlying biologic basis of Ph+ ALL provided an opportunity to develop a targeted approach to treatment of these patients. In this study, we showed that imatinib could be safely integrated into an intensive multiagent chemotherapy regimen. The outcome observed among cohort 5 patients treated with intensive imatinib dosing in combination with intensive chemotherapy is dramatically better than that observed in either historical controls from prior POG trials or trials reported by a large international collaborative group.[21] Although sample size is limited, there was no suggestion that patients who received either HLA-identical related- or unrelated-donor BMT fared better than those treated with intensive chemotherapy plus intensive imatinib dosing. At the time of this report, more than 80% of the patients with Ph+ ALL enrolled in AALL0031 have completed protocol therapy, and relapse after completion of therapy has not been observed. Longer follow-up is required to definitively evaluate whether this outstanding outcome is maintained.

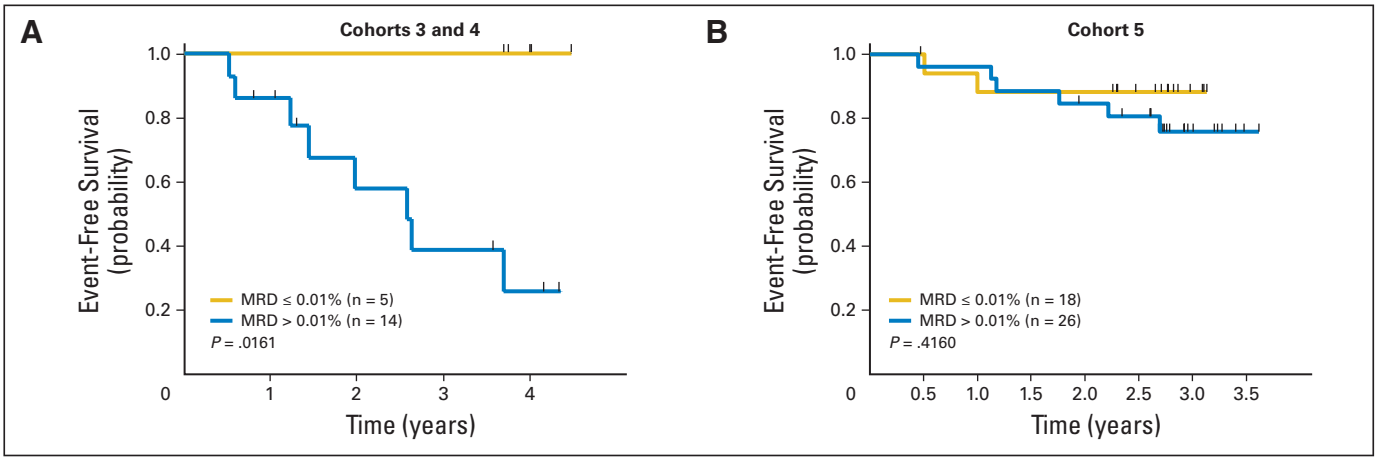

Fig 6. Impact of minimal residual disease (MRD) at study entry on outcome in Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL). (A) Event-free survival (EFS) by MRD at study entry (≤ 0.01% *v* > 0.01%) for cohorts 3 and 4 (100% *v* 38.6% ± 15.1%; *P* = .02). (B) EFS by MRD at study entry for cohort 5 (88.2% ± 17.5% *v* 75.9% ± 14.1%; *P* = .41). Induction failures were excluded from these analyses.

This study demonstrated the prognostic impact of MRD in Ph+ ALL at lower imatinib dosing (cohorts 3 and 4). More importantly, intensive dosing with imatinib in cohort 5 appeared to improve the expected outcome in both higher MRD and in induction failure patients. Together, these findings suggest that targeted tyrosine kinase inhibitor therapy can improve the prognosis of patient subsets that have historically had a poor outcome.

Previous studies have suggested that imatinib may improve post-allogeneic BMT outcomes for Ph+ patients.[15] In this study, imatinib treatment started between 4 and 6 months post-BMT and continued for 6 months. Unlike in a previous study,[15] no myelosuppression requiring imatinib dose reduction was observed.

We observed no major toxicities induced by continuous dosing of imatinib at 340 mg/m^2/d in combination with intensive chemotherapy. Although we did observe ALT elevation in maintenance therapy, it was addressed by decreasing the imatinib exposure from 21 to 14 days during each 4-week maintenance chemotherapy cycle. Imatinib-related left ventricular dysfunction and heart failure has been seen in adults,[25,26] but there was no signal for increased detection with imatinib compared with the control group in this study.

Newer tyrosine kinase inhibitors including dasatinib and nilotinib appear to have more potent suppression of BCR-ABL kinase activity.[27,28] These agents in combination with intensive chemotherapy may further improve the outcome of children with Ph+ ALL. The follow-up COG study for Ph+ ALL will use dasatinib because of the addition of Src inhibition.[29] The relative lack of adverse effects with imatinib may not be the same as with dasatinib, which is associated with pleural effusions.[30]

In conclusion, intensive dosing with imatinib, in addition to dose-intensive ALL chemotherapy more than doubled the 3-year EFS for children and adolescents with Ph+ ALL, with minimal toxicities. There was no suggestion that outcomes were superior with either HLA-identical or unrelated-donor BMT compared with chemotherapy plus imatinib. Additional follow-up is needed to determine the best long-term treatment for children with Ph+ ALL, but our results indicate that therapy should include a tyrosine kinase inhibitor, such as imatinib.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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