REGULAR ARTICLE

blood advances

Dasatinib and dexamethasone followed by hematopoietic cell transplantation for adults with Ph-positive ALL

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Key Points

- Dasatinib and dexamethasone induction then allogeneic hematopoietic cell transplantation was feasible and effective for untreated Ph^+ ALL.
- Treatment failure was associated with BCR-ABL1 T315I mutation, the p210 BCR-ABL1 isoform, or isolated CNS relapse.

Post-remission strategies after dasatinib-corticosteroid induction in adult Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL) are not well studied. We evaluated dasatinib and dexamethasone induction then protocol-defined post-remission therapies, including hematopoietic cell transplantation (HCT). Adults (N = 65) with Ph-positive ALL received dasatinib-dexamethasone induction, methotrexate-based central nervous system (CNS) prophylaxis, reduced-intensity conditioning (RIC) allogeneic HCT, autologous HCT, or chemotherapy alone, and dasatinib-based maintenance. Key end points were disease-free survival (DFS) and overall survival (OS). The median age was 60 years (range, 22-87 years). The complete remission rate was 98.5%. With a median follow-up of 59 months, 5-year DFS and OS were 37% (median, 30 months) and 48% (median, 56 months), respectively. For patients receiving RIC allogeneic HCT, autologous HCT, or chemotherapy, 5-year DFS were 49%, 29%, and 34%, and 5-year OS were 62%, 57%, and 46%, respectively. Complete molecular response rate after CNS prophylaxis was 40%. Relative to the p190 isoform, p210 had shorter DFS (median 10 vs 34 months, $P = .002$) and OS (median 16 months vs not reached, $P = .05$). Relapse occurred in 25% of allogeneic HCT, 57% of autologous HCT, and 36% of chemotherapy patients. T315I mutation was detected in 6 of 8 marrow relapses. Dasatinib CNS concentrations were low. Dasatinib-dexamethasone followed by RIC allogeneic HCT, autologous HCT, or chemotherapy was feasible and efficacious, especially with RIC allogeneic HCT. Future studies should address the major causes of failure: T315I mutation, the p210 BCR-ABL1 isoform, and CNS relapse. This study was registered at www.clinicaltrials.gov as #NCT01256398.

Introduction

In adult patients with Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL), adding the first-generation *BCR-ABL1*–targeted tyrosine kinase inhibitor (TKI) imatinib to chemotherapy yielded improved response and survival compared with chemotherapy alone due to more imatinib-treated patients

Submitted 22 March 2021; accepted 24 May 2021; prepublished online on *Blood Advances* First Edition 7 September 2021; final version published online 18 November 2021. DOI 10.1182/bloodadvances.2021004813.

Presented in part at the Annual Meeting of the American Society of Hematology, 2 December 2016, San Diego, CA and 28 November 2018, San Diego, CA.

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The full-text version of this article contains a data supplement.

proceeding to hematopoietic cell transplantation (HCT).[1-5] Second-generation TKIs appear to have further improved survival,[6-9] but myeloablative (MA) allogeneic HCT still may be the optimal postremission therapy.[10] MA autologous HCT and reduced-intensity (RIC) allogeneic HCT have shown efficacy and are appealing for older or less fit patients. Autologous HCT has shown similar outcomes to allogeneic HCT and superior outcomes to chemotherapy, with 4- to 5-year DFS of 46% to 80%.[2,5,11,12] Similarly, RIC allogeneic HCT for ALL yields 2- to 3-year survival of 39% to 48%, non-relapse mortality (NRM) of 21% to 25%, and relapse rates of 40% to 49%.[13-16] The efficacy of allogeneic HCT is likely due in part to graft-versus-leukemia effect.[17-19]

Prior studies support reduced-intensity (RI), TKI-based induction for Ph-positive ALL, yielding complete response (CR) rates of 95% to 100% and nearly no induction deaths.[5,20-23] GRAAPH-2005, comparing RI induction with imatinib, dexamethasone, and vincristine to imatinib with HyperCVAD (hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone alternating with high-dose methotrexate and high-dose cytarabine), showed a superior CR rate due to less induction death with the RI approach.[5] In LALA1205, dasatinib and prednisone induction followed by investigator-chosen postremission therapy yielded a CR rate of 100%, but relapse was common without subsequent allogeneic HCT or intensive chemotherapy.[22]

Relapse after second-generation TKI-based therapy is primarily due to clones with the BCR-ABL1 T315I resistance mutation, as seen in 71% to 75% of relapses after dasatinib.[22,24] Chemotherapy or HCT may eliminate these clones, and this likely accounts for the superior outcomes seen with intensive postremission strategies.[9,22,23] Recent reports suggest that ponatinib, which inhibits BCR-ABL1 T315I, together with corticosteroids or chemotherapy but without consolidative HCT, appears to be highly effective.[25,26]

Here, we present results of Cancer and Leukemia Group B (CALGB) 10701, a prospective study of Ph-positive ALL treatment using induction with dasatinib and dexamethasone followed by high-dose methotrexate–based central nervous system (CNS) prophylaxis and allocation to RIC allogeneic HCT, MA autologous HCT, or chemotherapy alone based on donor availability and patient age.

Methods

Patients

Patients were enrolled from December 2010 to November 2014 at 17 US centers. Eligible were adults ages ≥18 years with Ph-positive ALL defined by the t(9;22)(q34;q11) or 3-way variant by metaphase cytogenetics, *BCR-ABL1* by fluorescence in situ hybridization, and/or *BCR-ABL1* by reverse transcription polymerase chain reaction (RT-PCR). Prior therapy was excluded except for ≤1 week of corticosteroids and/or hydroxyurea. Eligible patients had adequate cardiac function.

Design

The study was a phase 2, 3-arm, nonrandomized trial (NCT01256398) with primary objectives to estimate DFS and OS of the whole population. The goal was to establish relevant baseline survival and toxicity data to inform future study design. Sample size was based on safety/feasibility. Considering a treatment-related mortality rate >0.4 as unacceptable and <0.2 as acceptable, 60 evaluable patients would yield 92% power with a 2-sided α of .05. All participating sites acquired institutional review board approval prior to enrolling patients. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Treatments

Induction (course I) used dexamethasone 10 mg/m^2 per day orally or IV days 1 to 7 and dasatinib 140 mg orally daily. A bone marrow biopsy was performed on day 15. If the day 15 marrow had ≤20% lymphoblasts, course II continued dasatinib 140 mg oral daily with another 7 days of dexamethasone as in course I. If the day 15 marrow had >20% lymphoblasts, patients also received vincristine and daunorubicin. Patients not in CR or CRi (CR with incomplete count recovery) on bone marrow biopsy after course II received a second induction course (course III) with dasatinib, cyclophosphamide, vincristine, daunorubicin, and dexamethasone. Patients in CR/CRi after course II/III proceeded to course IV. CNS prophylaxis (course IV) used IV vincristine and IV methotrexate 1000 mg/m^2 (n = 5) or 500 mg/m^2 (after 21 May 2012; n = 50), oral methotrexate, and 3 doses of intrathecal methotrexate. Course V consisted of HCT or chemotherapy alone. Patients 18 to 70 years underwent RIC allogeneic HCT if they had a 6/6 or 5/6 HLA-matched sibling or 8/8 HLA-matched unrelated donor. Otherwise, they underwent autologous HCT. Allogeneic HCT conditioning used fludarabine 30 mg/m^2 per day IV on days −7 through −3, alemtuzumab 20 mg/day IV on days −7 through −3, and melphalan 140 mg/m^2 IV once on day −2. Graft-versus-host disease (GVHD) prophylaxis with tacrolimus began on day −2. Patients undergoing autologous HCT received etoposide 10 mg/kg per day (age >65 years, 5 mg/kg per day) continuous IV for 4 days and cytarabine 2 g/m^2 (age >65 years, 1 g/m^2) IV every 12 hours for 8 doses followed by filgrastim for mobilization. Autologous HCT conditioning was melphalan 100 mg/m^2 per day IV on days −2 and −1. Patients >70 years or unable to undergo HCT received etoposide/cytarabine alone. Dasatinib maintenance (course VI, HCT cohorts) or dasatinib with mercaptopurine, vincristine, methotrexate, and dexamethasone (POMD; chemotherapy cohort) began on day 30 of course V and continued for ≥12 months and until 2 consecutive negative BCR-ABL1 RT-PCR assay results 3 months apart or relapse (Figure 1; supplemental Figure 1).

End point assessment

Hematologic, cytogenetic, and molecular responses were assessed locally. A CR required an absolute neutrophil count (ANC) >1 × 10^3/μL, platelets >100 × 10^3/μL, no circulating blasts, adequate marrow cellularity with trilineage hematopoiesis and <5% blasts, resolution of extramedullary disease, and transfusion independence. CRi was identical to CR except for ANC <1000/μL or platelets <100 000/μL. Complete cytogenetic remission (CCyR) required no clonally abnormal cells in ≥20 marrow metaphases. Complete molecular remission (CMR) required no detectable *BCR-ABL1* transcripts in a quantitative RT-PCR assay with a sensitivity of ≥1:10 000. Major molecular remission (MMR) required a ratio of *BCR-ABL1* transcripts to *ABL1* transcripts of ≤0.1%. Relapse was defined as the reappearance of lymphoblasts in the blood, marrow (>5%), cerebrospinal fluid (CSF), or other extramedullary site after a CR/CRi. *BCR-ABL1* isoform and *ABL1* kinase domain (KD) mutation determinations were performed locally and collected retrospectively. DFS was measured from CR/CRi to relapse or death, with patients censored at last

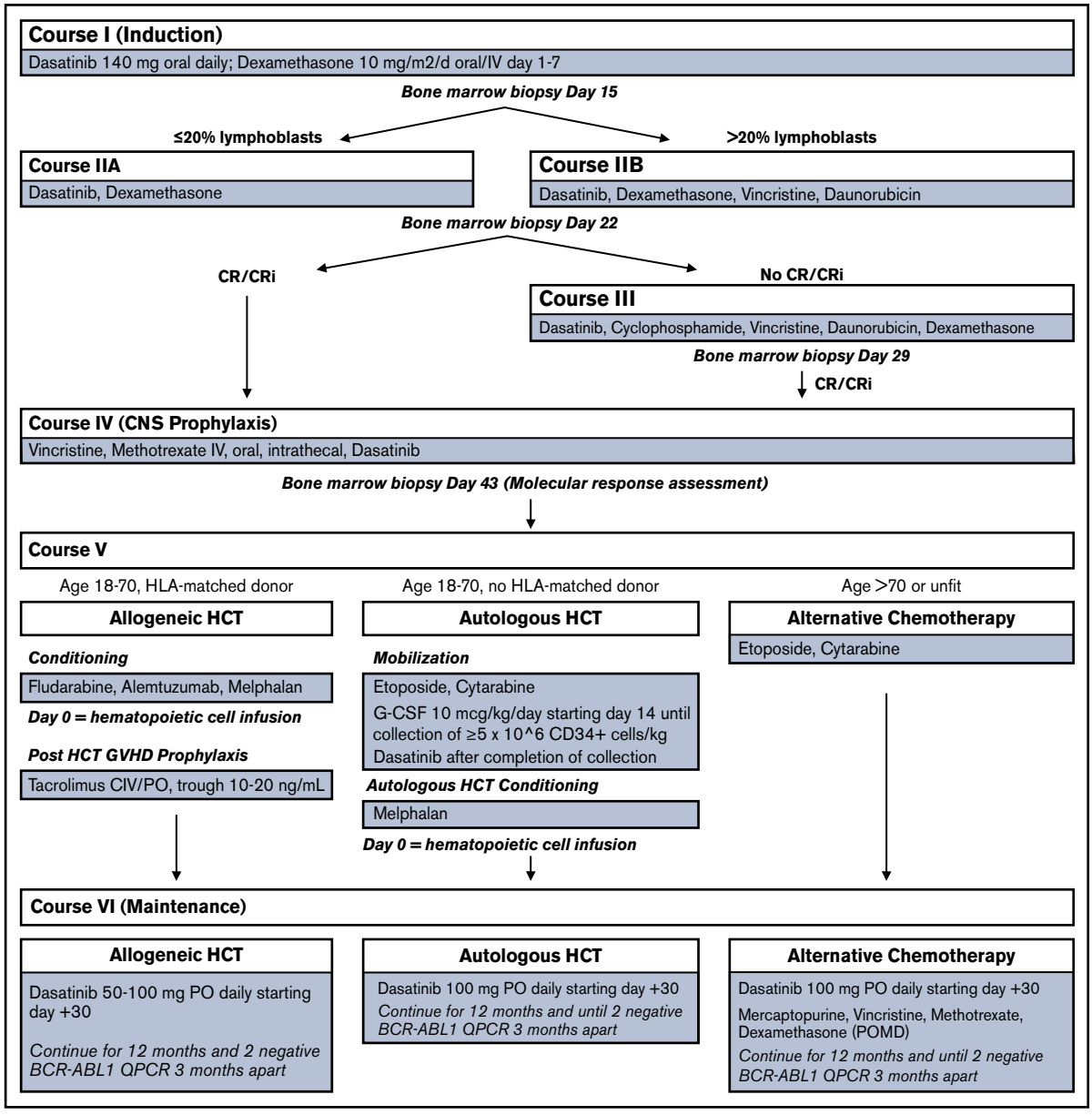

Figure 1. Treatment schema. CIV, continuous IV; G-CSF, granulocyte colony-stimulating factor; PO, by mouth; QPCR, quantitative RT-PCR.

time known to be alive and disease-free. OS was from therapy start to death, with patients censored at the last time known to be alive.

Dasatinib pharmacokinetics

Blood and CSF were collected in EDTA on day 15 of course I, 2 to 3 hours after oral dasatinib. Plasma was prepared by centrifugation of blood at 2000*g* for 5 minutes at 4°C and then frozen. CSF was processed similarly. Plasma dasatinib concentrations were quantitated by liquid chromatography tandem mass spectrometry.[27] For quantitation of low dasatinib CSF concentrations, the assay was modified. Specifically, the concentration range of 0.1 to 100 ng/mL was made in 50/50 PBS/plasma with a lower concentration of internal standard (100 ng/mL). CSF was diluted 1:1 in control plasma. Detection used an ABI SCIEX (San Jose, CA) 4000Q hybrid linear ion trap tandem mass spectrometer with electrospray ionization operated in the positive and multiple reaction monitoring mode. The high-performance liquid chromatography system and mass spectrometer were controlled by and data collected with Analyst software (version 1.4.2). The analyte-to-internal standard ratio was calculated for each standard by dividing the area of analyte peak by the area of the respective internal standard peak for the sample. Standard curves of analytes were constructed by plotting the analyte-to-internal standard ratio vs the known concentration of analyte in each sample. Standard curves were fit by linear regression with weighting by $1/y^2$, followed by back calculation of unknown concentrations. Under these conditions, the assay was linear, accurate (95.3% to 106.0%), and precise (2.51% to 6.75%) in the range of 0.1 to 100 ng/mL. α1-Acid glycoprotein (orosomucoid; AGP) was quantitated

by ELISA kits (R&D Systems, catalog #DAGP00) and AssayPro (catalog #EG5101-1), respectively. All samples were tested in duplicate.

Statistical analysis

The analysis population was eligible patients receiving ≥1 dose of dasatinib. The primary end points were DFS and OS. Secondary end points were DFS and OS of the course V cohorts, the efficacy of dasatinib maintenance, the ability to collect peripheral blood hematopoietic stem cell collection after dasatinib, the safety and efficacy of HCT after dasatinib, the safety and efficacy of dasatinib maintenance, and the correlation between plasma and CSF levels of dasatinib. For secondary end points, proportions were estimated based on the combined and individual course V cohorts. Time-to-event distributions were estimated using the Kaplan-Meier methods and compared using log-rank tests.[28] Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model.[29] Subgroup analyses were further conducted by age, BCR-ABL1 transcript, molecular response at the end of course IV, and dasatinib concentrations in plasma and CSF. A competing risk analysis, with death in remission as a competing risk, was used to compute the cumulative incidence for relapse among patients achieving a CR/CRi. End points, whenever scientifically plausible, for each cohort were compared in an exploratory fashion. All analyses were conducted with 2-sided tests and a significance level of .05 on the study database frozen on 17 October 2019. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

Results

Patient characteristics and disposition

Median age was 60 years (range, 22-87 years). *BCR-ABL1* isoform data were available for 50 patients (p190 in 76% and p210 in 24%) (Table 1). Of 65 patients starting course I, 60 achieved <20% marrow lymphoblasts on day 15, 1 had >20% lymphoblasts, 3 did not tolerate course I, and 1 was removed. Fifty-five patients entered course IV. Thirty-eight patients entered course V, with 20 allocated to allogeneic HCT, 7 to autologous HCT, and 11 to chemotherapy. Eleven patients underwent off-study allogeneic HCT in CR1, 2 after course IIA, 6 after course IV, 1 after course V chemotherapy, 1 during course VI chemotherapy, and 1 after autologous HCT due to engraftment failure. Two patients relapsing after autologous HCT underwent allogeneic HCT. Five patients skipped course V and then continued to course VI chemotherapy maintenance (Figure 2).

Response

The overall CR rate (CR + CRi) was 98.5%. Of 64 patients achieving CR/CRi, 36 patients (55%) achieved CR/CRi after course I, 27 (42%) after course IIA, and 1 (2%) after course III. Of 43 patients with molecular testing reported, 17 (40%) had CMR and 12 (28%) had MMR by the end of course IV. The CCyR rate was 79%. Of 8 patients with the p210 isoform, 1 achieved CMR and 1 MMR by the end of course IV (Table 2).

Table 1. Patient and disease characteristics (N = 65)

Patient and disease characteristics	n (%)
Age (y)	
Median (range)	60 (22-87)
Gender	
Female	33 (50.8)
Race	
White	55 (84.6)
Black	3 (4.6)
Asian	3 (4.6)
American Indian or Alaska native	1 (1.5)
Not reported/unknown	3 (4.6)
Ethnicity	
Not Hispanic or Latino	50 (76.9)
Hispanic or Latino	10 (15.4)
Unspecified	5 (7.7)
ECOG performance status (n = 64)	
0	16 (25)
1	38 (59.4)
2	10 (15.6)
Presenting WBC ($\times 10^3/\mu L$)	
Median (range)	23 (0.3-434)
BCR-ABL1 transcript (n = 50)	
p190	38 (76)
p210	12 (24)
Additional karyotypic abnormalities (n = 35)	
None	10 (28.6)
1	9 (25.7)
2-5	8 (22.9)
>5	8 (22.9)
Monosomy 7 ±others	7 (20)
Therapy for prior malignancy	
None/not reported	56 (86.2)
Chemotherapy	2 (3.1)
Radiation therapy	5 (7.7)
Chemotherapy and radiation therapy	1 (1.5)
Unknown treatment	1 (1.5)

Data are presented as n (%) of patients, unless otherwise indicated.
ECOG, Eastern Cooperative Oncology Group; WBC, white blood cells.

DFS and OS

With a median follow-up of 59 months (range, 38-90 months), the 5-year DFS was 37% (95% CI, 25% to 49%), and 5-year OS was 48% (95% CI, 35% to 61%, Figure 3). In landmark analyses starting from course V, DFS at 5 years was 49% for allogeneic HCT, 29% for autologous HCT, and 34% for chemotherapy alone, whereas OS at 5 years was 62%, 57%, and 46%, respectively. Median DFS for allogeneic HCT was 42 months vs 15 months for autologous HCT and 28 months for chemotherapy alone. Three of 7 autologous HCT patients underwent subsequent allogeneic HCT, 2 for relapse and 1

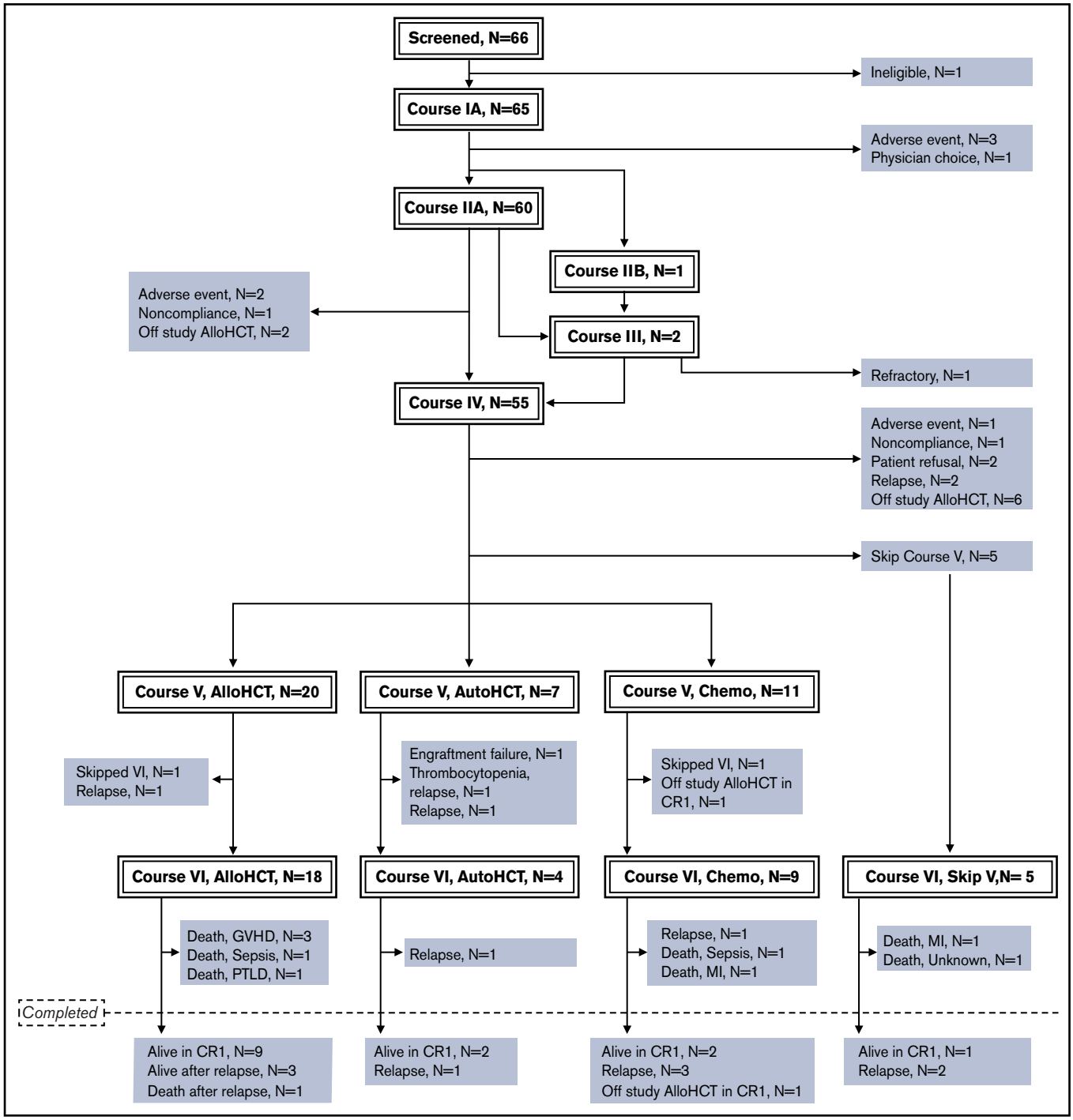

Figure 2. Patient disposition. MI, myocardial infarction.

for engraftment failure. Compared with the p190 isoform, the p210 isoform was associated with worse DFS (5-year DFS, 8% vs 41%, $P = .002$) and worse OS (5-year OS, 17% vs 53%, $P = .05$, Figure 3). Age (≤60 vs >60 years), CMR at end course IV (yes vs no), and receiving an allogeneic HCT (any vs none) did not impact DFS or OS. See supplemental Figure 2 for a swim plot of all patients.

Dasatinib maintenance

Of 43 patients continuing on protocol therapy after course IV, including 5 patients who skipped course V, 36 (84%) proceeded to dasatinib maintenance on protocol (Figure 2). Two patients relapsed during maintenance, 1 with the T315I mutation and 1 with isolated CNS relapse. Maintenance was completed by 25 patients, with 10 (40%)

Table 2. Response and relapse (N = 65)

Total	n	%
Overall CR (CR + CRi)*	**64**	**98.5**
CR	62	95.4
CR with incomplete count recovery	2	3.1
Refractory	1	1.5
Overall CR by course	**64**	
I (n = 65)	36†	55.4
IIA (n = 60)	27	41.5
IIB (n = 1)	0	0
III (n = 2)	1	1.5
Molecular response end of course IV	**43**	
CMR	17	39.5
MMR	12	27.9
Less than MMR	14	32.6
Cytogenetic response end of course IV	**34**	
CCyR	27	79.4
Less than CCyR	7	20.6
Relapse during each course	**25**	
I	0	0
IIA/IIB/III	0	0
IV: CNS prophylaxis	2	8
V	3	12
Allogeneic HCT (n = 20)	1	
Autologous HCT (n = 7)	2	
Chemotherapy (n = 11)	0	
VI: maintenance	2	8
Allogeneic HCT (n = 18)	0	
Autologous HCT (n = 4)	1‡	
Chemotherapy (n = 9)	1§	
Follow-up after completion of maintenance	10	40
Allogeneic HCT (n = 13)	4‡(1),§(1)	
Autologous HCT (n = 3)	1	
Chemotherapy (n = 6)	3‡ (1),§(1)	
Skipped course V (n = 3)	2	
Off-protocol therapy	8	32
Adverse events	4	
Patient refusal/noncompliance	3‡ (1)	
Off-protocol allogeneic HCT	1‡	

The bold are the categories of outcomes that are broken down below each bold category/outcome.

*Before course IV.

†Four patients who started course I achieved CR with alternative TKI or chemotherapy without progression.

‡T315I.

§Isolated CNS relapse.

relapsing after completion. Of these, 2 were isolated CNS relapses, and of 2 marrow relapses tested, both had the T315I mutation.

Relapse and BCR-ABL1 KD mutation

Overall, 25 patients relapsed with 5 CNS relapses (3 isolated) (Table 2). Eighteen relapses (72%) occurred off treatment. No relapses occurred prior to course IV. Relapse occurred in 25% of allogeneic HCT, 57% of autologous HCT, and 36% of chemotherapy patients. Of 36 patients entering maintenance, 9 died in remission, 2 relapsed on maintenance, and 10 relapsed after completion of maintenance. The cumulative incidence of relapse was not significantly different among the 3 course V cohorts (compared with chemotherapy, allogeneic HCT: HR, 0.62; 95% CI 0.18-2.12; autologous HCT: HR, 2.45; 95% CI 0.54-11.02). Two patients relapsing after autologous HCT underwent allogeneic HCT and are alive in remission. For 43 patients with end of course IV molecular response data, relapse occurred in 5 out of 17 (29%) with CMR, 2 out of 12 (17%) with MMR, and 8 out of 14 (57%) with less than an MMR. Of 12 patients with the p210 isoform, 9 (75%) relapsed, 2 (17%) died in remission, and 1 (8%) survives in CR. Of 37 patients with the p190 isoform in CR, 11 (29%) relapsed, 11 (29%) died in remission, and 15 (41%) survive in CR. Of 8 marrow relapses tested, 6 had the T315I mutation (75%) and 2 had no *ABL1* KD mutation. Whereas both patients relapsing without a T315I were off treatment at relapse, 4 of 6 with a T315I mutation relapsed on treatment.

Tolerability

Five patients discontinued during dasatinib/dexamethasone induction due to adverse events, including hyperglycemia, pulmonary infiltrates, fluid overload, sepsis, and prolonged QTc. No on-treatment deaths occurred until course V. Fifteen patients died in CR, 9 from complications after allogeneic HCT and 6 while on dasatinib or dasatinib/POMD (3 myocardial infarction/cardiac arrest, 1 stroke, 1 neutropenic sepsis, and 1 unknown). RIC allogeneic HCT was judged to be feasible, with 5 deaths (25%) from transplant-related complications (3 GVHD, 1 sepsis, and 1 posttransplant lymphoproliferative disorder). All 7 autologous HCT patients had robust hematopoietic stem cell mobilization (median, 92.5 $\times$ 10^6 $CD34^+$/kg; range, 30.6-886). Surprisingly, 2 of 7 autologous HCT patients failed to fully engraft (1 no engraftment and 1 prolonged thrombocytopenia) followed by salvage allogeneic HCT in one and relapse in the other. Both had the p210 isoform. Dasatinib maintenance was tolerable, with 72%, 80%, and 80% receiving at least 50% of planned maintenance doses in the allogeneic HCT, autologous HCT, and chemotherapy arms, respectively.

Dasatinib concentrations in plasma and CSF

The median plasma dasatinib concentration was 52.4 ng/mL (range, <lower limit of quantitation [LLQ]-308) with a median AGP concentration of 1170 μg/mL (range, 482-9920; n = 40). The median CSF dasatinib concentration was 0.348 ng/mL (range, <LLQ-1.37) with a median AGP concentration of 12.1 μg/mL (range, 2.99-46; N = 39). Based on the samples with dasatinib concentrations above the LLQ in plasma (n = 35) and CSF (n = 31), we could calculate CSF/plasma ratios in 28 patient samples. Median CSF dasatinib concentrations were 0.66% of the plasma dasatinib concentration (range, 0.09% to 15.8%). DFS and OS were shorter with plasma dasatinib concentrations less than the median (30.3 ng/mL, the median value when imputing zero for <LLQ, n = 5), although not statistically significant (5-year DFS, 32% vs 42%, $P = .28$; 5-year OS, 37% vs 60%, $P = .13$, respectively; Figure 3).

Discussion

In adult Ph-positive ALL, adding cytotoxic chemotherapy to TKIs with corticosteroids in induction does not improve hematologic response but does increase early mortality.[5] Supporting previous studies,[20-22,24,25] we observed a CR/CRi rate of 98.5% with

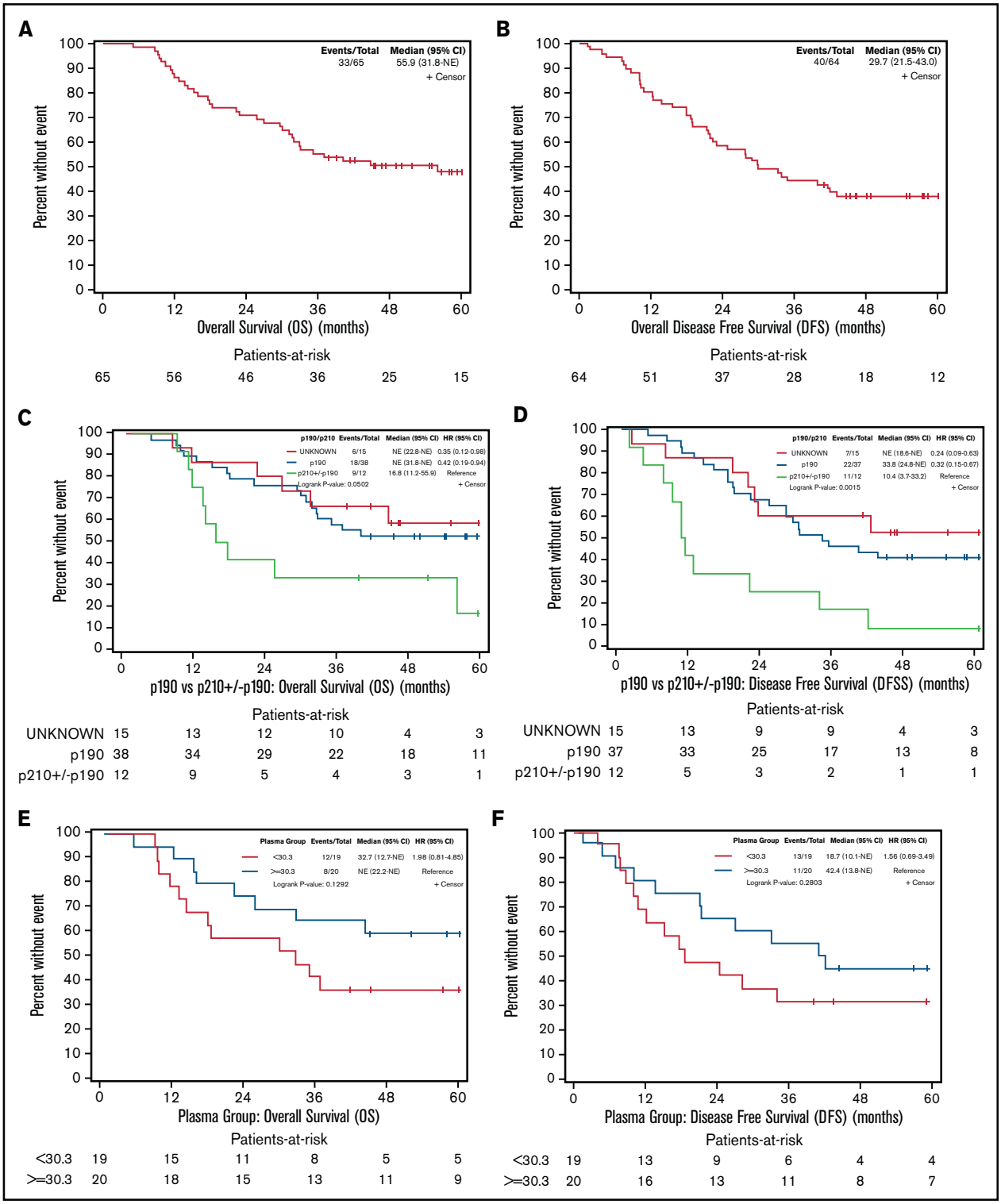

Figure 3. OS and DFS. OS (A) and DFS (B) for the entire cohort. OS (C) and DFS (D) by p190 vs p210 BCR-ABL1 isoform status. OS (E) and DFS (F) by plasma dasatinib levels.

dasatinib and dexamethasone induction, with no induction deaths. Without adequate postremission therapy, however, most patients relapse.[22] Of 6 patients on our study not receiving intensive postremission chemotherapy or HCT, only 1 remains alive in remission.

Until recently, intensive induction with cytotoxic chemotherapy plus a TKI has been a standard approach for Ph-positive ALL, although these regimens are associated with lower remission rates and higher early mortality than low-intensity induction with TKIs and corticosteroids

with or without vincristine.[4-10,25,30,31] The Southwest Oncology Group (SWOG) 0805 trial studied intensive treatment with Hyper-CVAD and dasatinib in younger patients (age, 18-60 years) with newly diagnosed Ph-positive ALL with patients allocated to myeloablative allogeneic HCT if they had a donor.[10] The CR/CRi rate was 88%, with 2 early deaths, in contrast to a 98.5% CR/CRi and no early deaths in our study supporting low-intensity induction as a safer and more effective induction option for newly diagnosed Ph-positive ALL. Patients on SWOG 0805 with a 10/10 HLA-matched donor were allocated to myeloablative allogeneic HCT followed by dasatinib maintenance. Compared with HyperCVAD plus dasatinib alone, transplanted patients had a superior relapse-free survival (3-year, 76% vs 51%, $P = .038$). Patients treated with RIC allogeneic HCT on this study had a somewhat lower relapse-free survival/DFS (3-year, 60%), although differences in disease and patient characteristics, including older age in this study, rather than the conditioning may account for the differences. Myeloablative conditioning remains the preferred approach for Ph-positive ALL in eligible patients, with RIC or nonmyeloablative conditioning being options for older or less fit patients. Randomized study is needed to better delineate optimal conditioning for Ph-positive ALL in the era of second- and third- generation TKIs.

Optimal postremission therapy after second-generation TKIs is still being determined, although nonrandomized studies support allogeneic HCT.[10,22,23] Unlike our study, however, prior studies of second-generation TKI plus corticosteroid induction have not specified postremission therapy.[22] Myeloablative conditioning has traditionally been preferred due to lower rates of relapse, but with high NRM.[15,16] Graft-versus-leukemia appears active in ALL, leading to a decreased risk of relapse with mild-moderate acute GVHD and chronic GVHD.[17-19] Thus, RIC may be a viable option, especially for older patients unlikely to tolerate myeloablative conditioning. Indeed, we observed a low relapse incidence with RIC allogeneic HCT, consistent with retrospective reports.[13-16] Autologous HCT is also efficacious for Ph-positive ALL,[2,5,11,12] but our study had too few patients undergoing autologous HCT to draw conclusions. In addition, 3 patients received allogeneic HCT after autologous HCT further limiting interpretation of a role for autologous HCT. A concerning finding is that 2 of 7 patients undergoing autologous HCT had engraftment failure, raising the possibility that dasatinib may negatively affect the engraftment potential of the hematopoietic cell product.

The recently published, nonrandomized GIMEMA LAL2116 D-ALBA study reported outcomes of dasatinib plus corticosteroid induction followed by blinatumomab in adults with newly diagnosed Ph-positive ALL. The CR rate was 98%, with a CMR rate of 60% after 2 cycles blinatumomab. With a relatively short (18-month) median follow-up, DFS and OS were 95% and 88%, respectively.[30] Our study, with a 59-month median follow-up, also reports favorable short- and long-term results with similar induction but more traditional postremission therapy approaches appropriate for older and less fit patients. Taken together, the results of our study and the D-ALBA study provide important information for clinical decision making and a potential randomized study to identify the optimal postremission approach for Ph-positive ALL, especially for older patients after dasatinib and corticosteroid induction.

The duration of dasatinib maintenance and optimal conditions for stopping dasatinib maintenance are not known. In this study, molecular response guided stopping of dasatinib, with a minimum of 1 year of maintenance. The relapse rate after stopping maintenance was 40% but was highly associated with T315I mutations and isolated CNS relapses, suggesting that more prolonged maintenance would have been unlikely to prevent relapse. Targeting T315I with ponatinib and improving CNS prophylaxis may improve outcomes with this regimen. Two ongoing studies show very low relapse rates with ponatinib with corticosteroids or HyperCVAD chemotherapy.[25,26]

Compared with the p190 isoform, the p210 isoform was associated with significantly worse DFS and OS. Worse DFS with p210 was also seen in CALGB 10001 (a similar trial using imatinib) and the GIMEMA LAL 1509 study of dasatinib and corticosteroid induction followed by chemotherapy or allogeneic HCT.[31,32] One reason may be that some p210 ALL patients represent CML in lymphoid blast crisis. Biologic differences and co-occurring mutations including Ikaros mutations were not assessed in this study and may contribute to the inferior outcomes in the p210 population.

In this study, plasma dasatinib concentrations were comparable to those expected (C_{max} [maximum concentration] of 56 [standard deviation 66] ng/mL at 1.5 h after a 100 mg dose).[33] The CSF AGP range was higher than the reported reference range of 1.5–4.5 μg/mL.[34,35] Based on the CSF concentrations and a K_d of dasatinib for AGP of 2.7 μM,[33] 70% to 97% of the CSF dasatinib would be unbound. In plasma, assuming 0.6 mM albumin and the AGP range, 1% to 3% of dasatinib would be unbound. The CSF/plasma dasatinib ratio of median 0.66% (range, 0.1% to 16%) therefore suggests that unbound plasma dasatinib concentrations are the main driving force for CSF concentrations. Dasatinib CSF concentrations were reported previously, but detectable concentrations of dasatinib were seen in only 6 patients. Only 3 patients had CSF/plasma ratios determined (reported as 5%, 8%, and 28%). The authors concluded that dasatinib CNS penetration was considerably higher than that of imatinib (brain penetrance, 0.5% to 2%).[36] Our large dataset from 39 patients without active CNS leukemia revealed that dasatinib CSF penetration is largely dependent on free plasma concentrations and is similar to imatinib.

Our results confirm the high efficacy and safety of induction with dasatinib and dexamethasone for Ph-positive ALL. RIC allogeneic HCT was feasible and effective after dasatinib-based therapy, and maintenance dasatinib was well tolerated after allogeneic HCT. As such, allogeneic HCT remains a standard of care for Ph-positive ALL and may be superior option after low-intensity induction. T315I mutation was the major cause of treatment failure and may be overcome by ponatinib or other targeted therapies such as blinatumomab in the future, potentially obviating the need for allogeneic HCT.

Acknowledgments

The authors acknowledge the technical expertise of Ken Czambel and John Schmitz in quantitating α1-acid glycoprotein concentrations. CALGB is now part of the Alliance for Clinical Trials in Oncology.

Authorship

Contribution: M.W., M.J.W., and R.A.L. designed the study, performed research, and collected data; M.J.W. and R.A.L. assembled, analyzed, and interpreted data and wrote the manuscript; J.Y. performed statistical analyses and edited the manuscript; E.S., J.H.B., S.M.C., and L.D.L. collected, assembled, analyzed, and interpreted data and edited the

manuscript; G.L.U., B.L.P., J.E.K., M.L., W.S., S.D., R.J.M., and R.M.S. collected data, interpreted data, and edited the manuscript; and all authors approved the final version of the manuscript.

Conflict-of-interest disclosure: M.J.W. has acted as an advisor to Gilead. G.L.U. has acted as a consultant to Jazz and Genentech and has received honoraria from Astellas. R.A.L. has acted as a consultant or advisor to Novartis, Amgen, Ariad/Takeda, Astellas, Celgene/Bristol-Myers Squibb, CVS/Caremark, Epizyme, and MorphoSys; has received clinical research support from Novartis, Astellas, Celgene, Cellectis, Daiichi Sankyo, Forty Seven, and Rafael Pharmaceuticals; and has received royalties from UpToDate. B.L.P. has acted as a consultant or advisor for Jazz and Rafael Pharmaceuticals and has received clinical research support from Genentech, Jazz, Novartis, Pfizer, and Rafael. J.H.B. received research support from Bristol-Myers Squibb. L.D.L. has received other clinical trial support from Novartis, Amgen, Bristol-Myers Squibb, and AbbVie and is a consultant to G1 Therapeutics and 7 Hills Pharm.

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