Title: Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia

Running Title: Complete molecular response in Ph+ ALL

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Key Points

- In patients with Ph+ ALL, achievement of CMR at 3 months is independently associated with improved survival
- CMR at 3 months may identify patients with Ph+ ALL who have excellent long-term outcomes without SCT in CR1

Abstract

The impact of achieving complete molecular response (CMR) in patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) remains undefined. We evaluated the impact of CMR on outcomes among 85 patients with Ph+ ALL who received frontline hyper-CVAD chemotherapy plus a tyrosine kinase inhibitor, had minimal residual disease (MRD) assessments for BCR-ABL1 by quantitative polymerase chain reaction both at complete remission (CR) and at 3-month time points and did not undergo allogeneic stem cell transplantation (SCT). MRD status at 3 months had better discrimination for overall survival (OS; P=0.005) and relapse-free survival (RFS; P=0.002) than did MRD status at CR (P=0.11 and P=0.04, respectively). At 3 months, achievement of CMR vs. response less than CMR was associated with longer median OS (127 months vs. 38 months, respectively, P = 0.009) and RFS (126 months vs. 18 months, respectively, P = 0.007). By multivariate analysis, only achievement of CMR at 3 months was prognostic for OS (HR 0.42 [95% CI 0.21-0.82], P=0.01). Patients with Ph+ ALL who achieve CMR at 3 months have superior survival compared to those with lesser molecular responses and have excellent long-term outcomes even when SCT is not performed.
Introduction

Assessment of minimal residual disease (MRD) has emerged as a powerful prognostic tool for patients with acute lymphoblastic leukemia (ALL).\textsuperscript{1-4} In patients with Philadelphia chromosome-negative (Ph-) ALL, MRD assessment can identify patients more likely to benefit from stem cell transplantation (SCT) in first complete remission (CR).\textsuperscript{5} However, the utility of MRD monitoring in patients with Philadelphia chromosome-positive (Ph+) ALL is less defined.\textsuperscript{6} In individual studies of chemotherapy plus a tyrosine kinase inhibitor (TKI) in patients with ALL, deeper molecular responses as assessed by quantitative polymerase chain reaction (PCR) for the \textit{BCR-ABL1} transcript have been associated with improved outcomes, suggesting that these patients may represent a group with better prognosis in whom SCT in CR1 may be avoided.\textsuperscript{7-9} Additionally, our previous retrospective analysis of patients receiving chemotherapy plus either imatinib or dasatinib who did not undergo SCT in CR1 found that achievement of at least a major molecular response (MMR) was independently prognostic for improved survival.\textsuperscript{10} To expand upon these findings, we sought to investigate the prognostic impact of achieving a complete molecular response (CMR) in adult patients with Ph+ ALL receiving frontline chemotherapy plus a TKI and compare that with lesser responses.

Methods

Patients

Between April 2001 and December 2015, 202 consecutive adult patients with previously untreated Ph+ ALL received induction with hyperfractionated cyclophosphamide,
vincristine, doxorubicin and dexamethasone alternating with methotrexate and high-dose cytarabine (the hyper-CVAD regimen) plus a TKI at our institution.\textsuperscript{11-13} The TKI was continued indefinitely as maintenance therapy. CR was achieved in 196 patients (97%), of whom 122 had MRD assessment for $BCR-ABL1$ by quantitative PCR both at CR and at 3 months as previously described.\textsuperscript{10} Thirty seven patients who underwent SCT in CR1 were excluded, leaving 85 patients evaluable for this analysis. Twenty three patients (27%) received imatinib, 39 (46%) received dasatinib and 23 (27%) received ponatinib. CR was achieved after 1 cycle of therapy in 98% of patients; only 2 patients required 2 cycles in order to achieve CR. Median duration of survivor follow-up was 44 months (range, 5-171 months). The treatment protocols were approved by the MD Anderson Cancer Center Institutional Review Board. Informed consent was obtained according to the Declaration of Helsinki and our institutional guidelines.

**Response Definitions**

CMR was defined as the absence of a detectable $BCR-ABL1$ transcript with a sensitivity of 0.01%. MMR was defined as a $BCR-ABL1/ABL1$ ratio $\leq 0.1\%$ on the International Scale for p210 $BCR-ABL1$ or a 3-log reduction in transcripts for p190 $BCR-ABL1$, but not meeting criteria for CMR. Relapse was defined by recurrence of $\geq 5\%$ blasts in a bone marrow aspirate or by the presence of extramedullary disease. Relapse-free survival (RFS) was calculated from the time of CR until relapse or death. OS was calculated from the time of treatment initiation until death.
Statistical Methods

RFS and OS were calculated using Kaplan-Meier estimates, and survival estimates were compared using the log-rank test. Univariate Cox proportional hazards regression models were used to assess the association between patient characteristics and RFS or OS. Patient characteristics with P<0.10 in the univariate models were included in the multivariate model; backward elimination was used until all predictors had a P<0.05.

Results and Discussion

Baseline characteristics are summarized in Supplemental Table 1. Molecular response at CR was CMR in 29 patients (34%), MMR in 10 (12%) and less than MMR in 46 (54%); molecular response at 3 months was CMR in 51 patients (60%), MMR in 16 (19%) and less than MMR in 18 (21%). Among patients with MMR at CR, 9 of 10 (90%) achieved CMR by 3 months, compared to only 14 of 46 patients (30%) with less than MMR at CR. CMR rate at CR for patients receiving imatinib, dasatinib, and ponatinib was 22%, 31% and 52%, respectively (P=0.25); CMR rate at 3 months was 39%, 54% and 87% for patients receiving each TKI, respectively (P=0.001).

MRD status at 3 months had better discrimination for OS (P=0.005) and RFS (P=0.002) than did MRD status at CR (P=0.11 and P=0.04, respectively; Figure 1A-D). At CR, OS or RFS did not differ between patients who achieved CMR and those with a lesser response (P = 0.26 and P = 0.15, respectively). A univariate analysis of factors predictive for RFS and OS is shown in Table 1. At 3 months, patients who achieved CMR had significantly longer median OS and RFS compared to those with a lesser
response (127 months vs. 38 months, HR 0.42 [95% CI 0.21-0.82], P = 0.01; and 126 months vs. 18 months, HR 0.43 [95% CI 0.21-0.78], P = 0.01, respectively). Twelve of 51 patients (24%) with CMR at 3 months experienced relapse with a median time to relapse of 16 months (range, 10-59 months); 10 of these patients subsequently achieved remission with salvage therapy and 5 underwent SCT in CR2. The 4-year OS and RFS rates for patients with CMR at 3 months were 66% and 63%, respectively. Only two deaths occurred after 4 years, both in patients who achieved CMR: one patient treated with dasatinib who relapsed with isolated CNS disease 5 years after initial diagnosis, and subsequently died from post-SCT infectious complications and one patient treated with imatinib who died from infection while in CR 10 years after initial diagnosis. Of the 7 patients who did not achieve CMR at 3 months and were still alive without relapse at 4 years, all eventually achieved CMR with a median time to CMR of 14 months (range, 8-87 months). Among the 51 patients who achieved CMR at 3 months, there was no impact on either OS or RFS according to TKI received (P=0.22 and P=0.40, respectively) or molecular response at CR (P=0.76 and P=0.85, respectively). By multivariate analysis, only the presence of Ph alone vs. Ph plus other chromosomal abnormalities (HR 0.42 [0.19-0.93], P=0.03) and CMR at 3 months (HR 0.41 [95% CI 0.21-0.82], P=0.01) were prognostic for RFS, and only CMR at 3 months was prognostic for OS (HR 0.42 [95% CI 0.21-0.82], P=0.01).

These findings suggest that patients with Ph+ ALL treated with frontline chemotherapy plus a TKI who achieve CMR by 3 months have excellent long-term survival, which is independent of any baseline factors or the TKI received. Among this cohort of patients
who did not receive SCT in CR1, the 4-year OS rate for patients achieving CMR by 3 months was 66% and median OS was over 10 years. The long-term survival for these patients compares very favorably to the historical survival rate of patients with Ph+ ALL.6,14 While these promising outcomes for this subgroup raise questions about whether SCT in CR1 can be safely avoided in these patients, definitive conclusions are limited due to potential bias influencing which patients were referred to SCT in CR1.

CMR rates vary based on the TKI that is added to chemotherapy, ranging from 28-50% with imatinib7,15,16, 45-65% with dasatinib9,12, and 78% with ponatinib13, and the survival rates achieved appear to be better with each successive generation of TKI, although no randomized trials have yet been performed to confirm this observation. In our cohort, the CMR rate at 3 months in patients who received ponatinib was more than 2-fold that of patients who received imatinib. While it is possible that the optimal timing of MRD assessment may vary across TKIs due to their varying potencies and different kinetics of leukemic burden reduction, these results nevertheless suggest that the impressive 2-year OS rate of 80% recently reported with hyper-CVAD plus ponatinib13 is likely mediated through the higher 3-month CMR rate achieved with this combination.

In conclusion, achievement of CMR at 3 months in patients with Ph+ ALL receiving frontline chemotherapy plus a TKI is associated with superior survival. Patients who fail to achieve CMR and do not undergo SCT in CR1 have relatively poor outcomes. Prospective trials employing MRD-based risk stratification for patients with Ph+ ALL may elucidate the optimal post-remission management of these patients.
Authorship Contributions

N.J.S. designed the study, collected and analyzed the data, and wrote the manuscript; E.J. and F.R. designed the study, collected and analyzed the data, treated patients, and wrote the manuscript; K.S. performed the statistical analysis; K.P. and R.L. performed the molecular analysis; H.K. designed the study, treated patients, and wrote the manuscript; R.G. and G.I. collected and analyzed the data; J.E.C., G.G-M, D.T., and S.M.O treated patients. All authors reviewed and approved the manuscript.

Disclosure of Conflicts of Interest

F.R., J.C. and H.K. have received research funding from Bristol Myers Squibb; J.C., E.J. and H.K. have received research funding from Ariad Pharmaceuticals; F.R., J.C., E.J. and H.K. have received research funding from Novartis Pharmaceuticals.

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References


Table 1. Univariate analysis for relapse-free and overall survival

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<th>Characteristics</th>
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<th>Risk of death</th>
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<td>0.37-0.94</td>
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<td>CMR at 3 months</td>
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<td>0.21-0.78</td>
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HR, hazard ratio; CI, confidence interval; WBC, white blood cell; PB, peripheral blood; BM, bone marrow; CNS, central nervous system; Ph, Philadelphia chromosome; TKI, tyrosine kinase inhibitor; CMR, complete molecular response

Figure legend

**Figure 1. Outcomes for patients based on molecular response.** Relapse-free survival by molecular response at (A) complete remission and at (B) 3 months. Overall survival by molecular response at (C) complete remission and at (D) 3 months.
Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia


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