Tyrosine Kinase Inhibitors as Initial Therapy for Patients With Chronic Myeloid Leukemia in Accelerated Phase

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Abstract

Some patients with chronic myeloid leukemia (CML) present with accelerated phase (AP) features at the time of diagnosis. We analyzed the outcome of 51 consecutive patients with de novo CML-AP who received tyrosine kinase inhibitors (TKIs) as initial therapy. Patients with de novo CML-AP have excellent outcomes with TKIs as initial therapy, particularly with second-generation TKIs (2GTKI).

Background: Accelerated phase CML most frequently represents a progression state in CML. However, some patients present with AP features at the time of diagnosis. There is limited information on the outcome of these patients who received TKIs as initial therapy. **Patients and Methods:** We analyzed the outcome of 51 consecutive patients with CML who presented with features of AP at the time of diagnosis, including blasts $\geq$ 15% (n = 6), basophils $\geq$ 20% (n = 22), platelets $< 100 \times 10^9$/L (n = 3), cytogenetic clonal evolution (n = 17), or more than 1 feature (n = 3). Patients received initial therapy with imatinib (n = 30), dasatinib (n = 5), or nilotinib (n = 16). **Results:** The rate of complete cytogenetic response for patients treated with imatinib was 80%, and with dasatinib or nilotinib was 90%. Major molecular response (MMR) (Breakpoint Cluster Region (BCR)-Abelson (ABL)/ABL $\leq$ 0.1%, International Scale [IS]) was achieved in 69% of patients including complete molecular response (BCR-ABL/ABL $\leq$ 0.0032% IS) in 49%. MMR rates for patients treated with imatinib were 63%, and with 2GTKIs, 76%. Overall survival at 36 months was 87% with imatinib and 95% with 2GTKIs. **Conclusion:** TKIs should be considered standard initial therapy for patients with AP at the time of diagnosis.

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the Breakpoint Cluster Region (*BCR*)-Abelson (*ABL*) fusion gene.[1] This fusion gene produces the constitutively activated tyrosine kinase *BCR-ABL,* the therapeutic target of *BCR-ABL* tyrosine kinase inhibitors (TKIs).[2] The disease usually evolves in a triphasic clinical course with an initial chronic phase (CP), followed by an intermediate accelerated phase (AP) and frequently a terminal blast phase (BP).[3]

Associated with cytogenetic instability, progressive impairment of myeloid cell differentiation, and eventually BP progression, AP CML (CML-AP) has an aggressive clinical course, historically associated with a median survival of only 6 to 18 months.[1,4,5] Approximately 5% to 10% of patients with CML present with AP features at the time of diagnosis.[4]

Imatinib, dasatinib, and nilotinib are standard initial TKI therapies for patients with CML in CP. Most studies exploring the use of TKIs for CML-AP have included patients progressing to AP after previous therapies have failed.[1] Little is known about the outcomes

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of patients with CML-AP features at the time of presentation who received initial therapy with imatinib[6-10] and there are no published data on nilotinib and dasatinib as initial therapy for de novo CML-AP. The aim of this study was to describe the efficacy of imatinib, dasatinib, and nilotinib as initial therapy for patients with de novo CML-AP.

Patients and Methods

Study Group

From September 1999 through May 2011, 51 adult patients (age $\geq$ 18 years) with a confirmed diagnosis of CML-AP were treated with TKIs as initial therapy in consecutive or parallel clinical trials and were included in this analysis. Patients with any of the following features of CML-AP were eligible: blasts $\geq$ 15% in peripheral blood (PB) or bone marrow (BM), blasts and promyelocytes $\geq$ 30% (PB or BM), basophils $\geq$ 20% (PB or BM), platelets $< 100 \times 10^9$/L unrelated to therapy, and/or cytogenetic clonal evolution.[4] The presence of any clonal abnormality other than a single Philadelphia chromosome (Ph), was classified as cytogenetic clonal evolution.[11]

Other inclusion criteria included Eastern Cooperative Oncology Group performance status 0 to 2, and acceptable end organ function including total bilirubin $< 1.5 \times$ upper limit of normal (ULN), serum glutamic pyruvate transaminase $< 2.5 \times$ ULN, creatinine $< 1.5 \times$ ULN). For women of childbearing potential, a negative pregnancy test was required for inclusion. Except for hydroxyurea, patients could not have received more than minimal therapy, defined as $<$ 1 month of previous interferon-alpha (with or without cytarabine) and/or imatinib (for patients receiving nilotonib or dasatinib).

Written informed consent was obtained from all patients, according to institutional guidelines. The protocols were approved by the M.D. Anderson Cancer Center Institutional Review Board and were executed in adherence to the Declaration of Helsinki.

Patient Evaluation

Patients were followed with complete blood counts every 1 to 2 weeks for the first 2 to 3 months, and then every 4 to 6 weeks. BM aspirations were performed at least every 3 months for the first 12 months, then every 6 to 12 months. Cytogenetic responses were also evaluated on those specimens. Response criteria for CML-AP have been previously described.[12] Briefly, a complete hematologic response (CHR) was characterized by the following: resolution of signs and symptoms of CML, normalization of the blast percentage in the PB and BM ($\leq$ 5% marrow blasts); leukocytes $< 10 \times 10^9$/L; normal PB differential (with no peripheral blasts, promyelocytes, or myelocytes); and platelet counts $< 450 \times 10^9$/L. If thrombocytopenia ($< 100 \times 10^9$/L) was present before treatment, then normalization of platelet counts to $> 100 \times 10^9$/L was required for a CHR. Patients with a normal platelet count before starting therapy, who developed thrombocytopenia $< 100 \times 10^9$/L as a consequence of TKIs could be considered to have achieved CHR if they had all the other features of CHR.[12]

Patients were evaluated for cytogenetic response using conventional cytogenetic analysis in 20 metaphases.[1] Cytogenetic responses were classified as minor if the percentage of Ph-positive metaphases was 36% to 95%, partial (PCyR) if 5% to 35%, and complete (CCyR) if 0%. A major cytogenetic response (MCyR) included a CCyR and PCyR (ie, $\leq$ 35% Ph-positive [Ph+] metaphases).

BCR-ABL transcripts were identified using real-time quantitative reverse transcription polymerase chain reaction analysis on PB and/or BM aspirate.[1] A major molecular response (MMR) was defined as BCR-ABL/ABL transcripts $\leq$ 0.1% assessed using the international scale (IS). A complete molecular response ($MR^{4.5}$) was defined as BCR-ABL/ABL $\leq$ 0.0032% (IS).[13]

Statistical Considerations

Categorical variables were analyzed using χ^2 and Fisher exact tests. Survival probabilities were estimated using the Kaplan-Meier method. The log-rank test was used for comparing survival estimates. Event-free survival (EFS) was measured from the date of start of therapy to the occurrence of an event. The following occurrences constituted an event: loss of CHR, loss of MCyR, transformation, and death (while participating in the study). Transformation-free survival (TFS) was calculated from the date treatment was started to the date of transformation to BP or death during participation in the study. Overall survival (OS) was measured from the date treatment started to the date of death at any time from any cause, or last follow-up. We also analyzed failure-free survival (FFS) where failure included an event (as defined above) or loss of CCyR, toxicity, or discontinuation for any reason.

Results

A total of 51 patients with the following features of AP at the time of diagnosis were included: blasts $\geq$ 15% (n = 6), basophils $\geq$ 20% (n = 22), platelets $< 100 \times 10^9$/L (n = 3), cytogenetic clonal evolution (n = 17), or more than 1 feature (n = 3). The median age was 46 years (range, 22-81 years); 55% were male (Table 1). Patient characteristics were similar in all treatment groups. Thirty (59%) patients received initial therapy with imatinib and 21 (41%) with a second-generation TKI (2GTKI) (16 received nilotinib and 5 dasatinib). Among the 30 patients treated with imatinib, 5 received an initial dose of 400 mg/d, 21 received 600 mg/d, and 4 $>$ 600/d (800 mg/d, n = 3; 1000 mg/d, n = 1). The starting dose of nilotinib was 800 mg daily (400 mg twice per day [b.i.d.]) and of dasatinib 100 mg daily (or 50 mg b.i.d.). The median time to initiate TKI therapy was 1 month from diagnosis (range, 0-10 months) (Supplemental table 1).

Responses, time to response, and median follow-up according to treatment cohort are shown in Table 2. After a median follow-up of

Table 1 Patient Characteristics

Characteristic	Value
Total Patients, n	51
Median Age (Range), Years	46 (22-81)
Median Months to Start TKIs (Range)	1 (0-10)
Male Sex, n (%)	28 (55)
AP Features, n (%)	
Increased basophils	22 (43)
Increased blasts	6 (12)
Clonal evolution	17 (33)
Decreased platelets	3 (6)
More than 1 factor	3 (6)

Abbreviations: AP = accelerated phase; TKI = tyrosine kinase inhibitor.