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Accelerated phase chronic myeloid leukemia: evaluation of clinical criteria as predictors of survival, major cytogenetic response and progression to blast phase

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ABSTRACT

Background: Published criteria defining the accelerated phase in chronic myeloid leukemia are heterogeneous and little is known about predictors of poor outcome.
Methods: This is a retrospective study of 139 subjects in the accelerated phase of chronic myeloid leukemia treated with imatinib at a single center in Brazil. The objective was to identify risk factors for survival, major cytogenetic response and progression to blast phase in this population. The factors analyzed were: blasts 10–29%, basophils $\geq$ 20%, platelets $> 1 \times 10^6/\mu L$ or $< 1 \times 10^5/\mu L$ and white blood cells $> 1 \times 10^5/\mu L$ in the peripheral blood, as well as clonal evolution, splenomegaly, hemoglobin < 10 g/dL, time between diagnosis of chronic myeloid leukemia and imatinib treatment, and hematologic toxicity.
Results: Risk factors for poor survival in multivariate analysis were Grades 3–4 hematologic toxicity (p-value = 0.001), blasts 10–29% (p-value = 0.023), and hemoglobin < 10 g/dL (p-value = 0.04). Risk factors for not achieving major cytogenetic response were blasts 10–29% (p-value = 0.007), hemoglobin < 10 g/dL (p-value = 0.001), and previous use of interferon (p-value = 0.032). Risk factors for progression to the blast phase were hemoglobin < 10 g/dL (p-value = 0.005), basophils $\geq$ 20% (p-value = 0.023), and time from diagnosis of chronic myeloid leukemia to imatinib treatment > 12 months (p-value = 0.030).
Conclusion: These data indicate that patients with the above risk factors have a worse prognosis. This information can guide the therapy to be used.

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Introduction

Chronic myeloid leukemia (CML) is a clonal disorder of hematopoietic stem cells characterized by the reciprocal translocation t(9;22)(q34;q11) which determines the Philadelphia chromosome and constitutive activation of the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase.[1,2] At the time of diagnosis, 90% of patients are in the chronic phase (CP). However, CML can progress from the CP to a more aggressive clinical picture – the accelerated phase (AP), when disease control is more difficult. AP is a signal of progression and transformation to the usually fatal blast phase (BP).

Over the past decade, the introduction of imatinib mesylate has been considered the first-line therapy for all phases of CML.[3–7] Clinical trials have established the efficacy of imatinib in targeting the pathophysiology of CML, resulting in increased survival and fewer side effects than with the use of interferon.[8–10] In Brazil, the delayed approval of imatinib mesylate for first line therapy led many patients to receive this therapy only at advanced phases of the disease. In the era of tyrosine kinase inhibitors, it is important to define prognostic factors not only prior to therapy but also during the course of treatment. The biological characteristics of the disease can strongly influence the degree and duration of response to imatinib and the overall survival (OS).

The criteria of the AP vary in the literature (Table 1). While some criteria are included in most classifications, such as percentage of basophils and blasts in the peripheral blood (PB), others are subjective and are included in only some classifications, e.g. persistent splenomegaly. The International Blood and Marrow Transplant (IBMTR) criteria have been used in studies that involved bone marrow transplantation.[11] In 2001 the World Health Organization (WHO) proposed a new classification system in order to refine the criteria for the AP and BP.[12] In 2006, the MD Anderson Cancer Center reclassified patients and compared their outcomes with imatinib as well, based on standard definitions and on the new WHO classification system.[6] The European Leukemia net (ELN) criteria were revised in 2013.[13]

Objective

The main purpose of this study was to identify which risk factors were associated with poor survival, with the lack of major cytogenetic response (MCR), and with progression to BP in a Brazilian AP-CML population from a single referral center.

Methods

This retrospective study, performed from January 2000 to November 2011, comprised 139 patients with AP-CML who were treated with imatinib at the hematopoietic stem cell transplant (HSCT) center of Hospital de Clínicas of the Universidade Federal do Paraná, Brazil. The WHO criteria are routinely used to evaluate patients with AP-CML at this center. However, as the objective of this study was to do an exploratory analysis of published risk factors, subjects were categorized with AP-CML if they had at least one of the aforementioned published criteria.[6,11–13] All patients received imatinib at an initial dose of 600 mg as first therapy for AP-CML. Doses were incremented (maximum of 800 mg) in cases of inadequate response or reduced (minimum of 300 mg) in cases of hematological or non-hematological toxicity, as necessary. This study was approved by the Ethics Committee of Hospital de Clínicas, Universidade Federal do Paraná, which waived the requirement of informed consent, as this was a retrospective study with collection of data from medical records.

The following risk factors, some of which were selected according to previously published criteria (Table 1), were evaluated: basophils $\geq$ 20% in PB, platelets > 1000×10^9/L unresponsive to therapy or < 100×10^9/L in PB, white blood cells (WBC) > 100×10^9/L in PB, blast 10–29% in PB, presence of clonal evolution (CE), hemoglobin <10 g/dL, and splenomegaly. Splenomegaly was considered when the spleen was palpable $\geq$10 cm from the left costal margin despite the use of hydroxyurea. Other clinical factors relevant to the disease were also analyzed, including the Sokal score > 0.8 (calculated at the time of diagnosis), time between diagnosis of CML and treatment with imatinib > 12 months, previous use of interferon, age > 60 years, and Grades 3–4 hematologic toxicity.

As the PB blasts cut-off point varies in the existing criteria, this study analyzed PB blasts as a continuum with death as the endpoint. A receiver operating characteristic (ROC) curve with death as the endpoint was designed to identify a cut-off value for the PB blast count.

Cytogenetic analysis was performed by the G-banding technique. Bone marrow specimens were examined on direct short-term (24-h) cultures with at least 20 metaphases being analyzed. BCR-ABL transcripts were detected by analyzing peripheral blood with quantitative real-time polymerase chain reaction (PCR) according to the International Scale.

Statistic analyses were performed using the STATA program version 8.0. Bivariate and multivariate analyses were performed using the Cox proportional hazards regression model. Variables with p-values < 0.20 in the bivariate analysis were included in the multivariate analysis model. A p-value < 0.05 was considered statistically significant. Disease free survival (DFS) was defined as the time from the beginning of treatment to loss of MCR.

The primary endpoint of this study was the identification of risk factors for survival. Risk factors for lack of MCR and transformation to BP were evaluated as secondary endpoints. The BP considered PB or marrow blasts $\geq$30%.

Results

One hundred and sixty-three patients in AP-CML were identified. Twenty-four patients treated with dasatinib or nilotinib were excluded. Thus, 139 AP-CML patients were treated with imatinib. Of these 139 patients, 60 (43.2%) patients who presented at this center with AP had only received hydroxyurea previously. The remaining 79 (56.8%) patients progressed from CP CML treated mainly with hydroxyurea or interferon alpha in isolation or with Ara-C. Of the 139 patients included, 62 (44.6%) were female and 77 (55.4%) were male. Median age was 43.6 years and 25 (18%) were >60 years of age. Forty-one patients (29.5%) died during the study follow-up and 22