Response and Adverse Effects of Nilotinib in Imatinib-resistant Chronic Myeloid Leukemia Patients: Data From a Developing Country

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ABSTRACT

Purpose: The purpose of this study was to determine the frequency of major cytogenetic response (MCyR) and adverse events with nilotinib in adults with imatinib-resistant Philadelphia chromosome–positive chronic myeloid leukemia (CML).

Methods: This is a descriptive cross-sectional study conducted at The Aga Khan University Hospital in Karachi from October 17, 2010, to October 17, 2011. A cytogenetic assessment using fluorescent in situ hybridization was performed on peripheral blood before initiation of treatment and 6 months after treatment with nilotinib. The frequency of adverse effects was assessed at 6 months, and the patient overall survival was calculated after 3 years.

Findings: This study enrolled 82 imatinib-resistant patients. The mean (SD) patient age was 38.9 (12.2) years. There were 62 patients (75.6%) in chronic phase, 15 patients (18.3%) in accelerated phase, and 5 patients (6%) in blast crisis phase. At 6 months cytogenetic studies were available for 40 (52%) of 77 patients, and MCyR was observed in 31 (77.5%) of 77 patients. The patients in chronic phase had the highest frequency of MCyR (n = 27 [87%] of 31). We observed 6 deaths (7.3%), and the overall survival at 3 years was 92.7%. There was isolated thrombocytopenia in 12 patients (15.6%). The most frequent nonhematologic adverse events were myalgia and headache.

Implications: The nilotinib response rates were higher in chronic phase patients, and the most common adverse events were thrombocytopenia, myalgia, and headache. (*Clin Ther.* 2015;37:2449–2457)

Key words: chronic myeloid leukemia, cytogenetic response, hematologic response, imatinib, nilotinib, overall survival.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1 to 2 cases per 100,000 people. CML accounts for 15% of newly diagnosed cases of adult leukemia.[1] Imatinib mesylate is an orally administered *BCR-ABL* tyrosine kinase inhibitor (TKI) that improves the outcome of CML.[2,3] Six months of imatinib therapy induces major cytogenetic response (MCyR) in 49.2% of cases[4] and complete cytogenetic response (CCyR) in 86% of patients with chronic phase CML.[5] Imatinib therapy in patients with accelerated and blast phase disease leads to reduced response rates, and patients relapse within 1 year.[6,7]

Approximately 3% to 4% of patients with chronic phase CML develop imatinib resistance annually.[8] The acquired resistance occurs via both *BCR-ABL*–dependent and *BCR-ABL*–independent mechanisms.[9] *BCR-ABL*–dependent mechanisms (mutations in the *ABL* kinase domain) are responsible for 40% to 50% of resistance cases.[9,10] Point mutations are the most frequent mutations (50%–52% of cases).[11,12] However, other highly resistant mutations have been found in the P-loop within or near residues that directly

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contact the drug (*A-loop* mutants and *T315I* mutation). The frequency of imatinib resistance in CML patients in Pakistan is not known.

Nilotinib is a new orally administered TKI that is 30-fold more potent than imatinib and is active against 32 of 33 imatinib-resistant *BCR-ABL* mutant cell lines.[13] The drug is approved by the National Comprehensive Cancer Network[14] as a second-generation TKI in imatinib-resistant patients with newly diagnosed chronic and accelerated phase CML.[15,16] The complete hematologic response (CHR) and MCyR rates for nilotinib were higher in imatinib-resistant patients with chronic phase disease than in patients with accelerated or blast phase disease.[10,17,18]

The CML clinic was established at the Aga Khan University and Hospital in 2003. The cost of nilotinib (200 mg) in Pakistan is US$32 per tablet. Most patients are unable to afford this medication because Pakistan is a developing country. In our institution, the Novartis Oncology Access Program provides financial assistance to patients requiring nilotinib treatment. Patients with CML who are prescribed nilotinib undergo a yearly financial evaluation, and depending on their socioeconomic status, the patient either receives nilotinib for free or pays for a fraction of the treatment. The purpose of this study is to determine the frequency of MCyR and adverse effects with nilotinib therapy in patients with imatinib-resistant CML. In this study, the age at the time of CML presentation is lower than that found in Western populations. Thus, our results may vary in terms of response and tolerability.

PATIENTS AND METHODS

This was a retrospective cohort study conducted at The Aga Khan University Hospital, Karachi. Eighty-two patients were enrolled in the study from October 16, 2010, to October 16, 2011.

Inclusion and Exclusion Criteria

We included patients with imatinib-resistant CML who were $\geq$18 years of age with normal baseline electrocardiography findings in all phases of disease. These patients were consecutively selected. When the imatinib-resistant patients were prescribed nilotinib, they were referred to the Novartis Oncology Access Program for financial support. The patients who were resistant to both first- and second-generation TKIs were given an option of allogeneic stem cell transplant depending on the availability of an HLA-matched donor. Imatinib resistance was defined using the following criteria: lack of CHR at or after 3 months; absence of minimal cytogenetic response (CyR) by 6 months or MCyR by 12 months; loss of CHR or minor CyR, MCyR, or CCyR; or development of clonal evolution. The highest dose of imatinib was 800 mg/d.

The patient exclusion criteria included age $<$18 years because nilotinib is not approved by the Food and Drug Administration for this age group and patients receiving medications known to prolong the QT interval. Patients were also excluded if they had a baseline QTc of $\geq$450 milliseconds because nilotinib is known to prolong the QT interval and treatment could lead to cardiac arrhythmias.[19]

Assessment of Response to Nilotinib Therapy, Frequency of Adverse Effects, and OS Rate

Imatinib-resistant patients were prescribed nilotinib at a dose of 400 mg twice a day. A cytogenetic assessment of peripheral blood cells by fluorescence in situ hybridization was performed before initiating drug treatment and 6 months after treatment with nilotinib. All patients were followed up in an outpatient clinic by the hematologist. These patients were assessed every 2 months, and a complete blood cell count was performed at each visit. Electrocardiography was performed to monitor the QTc interval at baseline and then 7 days after beginning nilotinib therapy. The patients were then examined by electrocardiography every 3 months. The cumulative adverse events were determined after 6 months. The overall survival (OS) was assessed after 3 years of follow-up and was calculated from the start of nilotinib therapy to death due to any cause.

Statistical Analysis

All time-to-event analyses were performed using the Kaplan-Meier method. The data are presented using descriptive statistics. The statistical package for social sciences 21 was used for data entry and analysis. The results are presented as number (percentage) and frequency for qualitative variables, such as cytogenetic response, sex, and adverse events. The results are reported as the mean (SD) for quantitative variables, such as age, complete blood cell count, and disease duration.