Original Study

Clinical Safety and Efficacy of Nilotinib or Dasatinib in Patients With Newly Diagnosed Chronic-Phase Chronic Myelogenous Leukemia and Pre-Existing Liver and/or Renal Dysfunction

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Abstract

Patients with CML-CP and mild to moderate renal or liver dysfunction can be safely treated with front-line dasatinib or nilotinib and can achieve similar outcome compared to those of patients with CML-CP without organ dysfunction.

Background: The safety and efficacy of front-line nilotinib and dasatinib in patients with newly diagnosed chronic-phase chronic myelogenous leukemia (CML-CP) with pre-existing liver and/or renal dysfunction are unknown. **Patients and Methods:** We analyzed the adverse event rates, response rates, and survival rates of 215 patients with CML-CP with or without renal and/or liver dysfunction who had been treated with front-line nilotinib (n = 108) or dasatinib (n = 107). **Results:** The overall median follow-up period was 49 months. At baseline, 6 dasatinib-treated patients (6%) had mild renal dysfunction and 13 (12%) had mild liver dysfunction. Also, 8 nilotinib-treated patients (7%) had mild renal dysfunction, 1 (1%) moderate renal dysfunction, and 9 (8%) mild liver dysfunction. No significant differences were found in the rate of complete cytogenetic response, major molecular response, or molecular response by a 4.5 log reduction on the international scale between the organ function cohorts. Dasatinib- or nilotinib-treated patients with baseline renal dysfunction had a greater incidence of transient reversible acute kidney injury ($P = .011$ and $P < .001$), and nilotinib-treated patients with renal dysfunction had a greater incidence of bleeding ($P < .001$). **Conclusion:** Patients with CML-CP and mild to moderate renal or liver dysfunction can be safely treated with front-line dasatinib or nilotinib and can achieve response rates similar to those of patients with CML-CP without organ dysfunction.

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Introduction

Nilotinib and dasatinib—orally administered selective tyrosine kinase inhibitors (TKIs) that target BCR-ABL kinase and several other kinases[1-3]—are standard front-line agents for patients with chronic myeloid leukemia (CML).[4-14] In the phase III, randomized, open-label, multicenter ENESTnd trial (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients) and the multinational randomized DASISION trial (DASatinib vs. Imatinib Study In treatment-Naïve CML patients), the efficacy and safety of nilotinib and dasatinib were compared with those of imatinib in patients with newly diagnosed CML in the chronic phase (CML-CP).[6] Analysis of the long-term follow-up data confirmed that, compared with imatinib, nilotinib and dasatinib induced a greater rate of molecular responses, the responses were deeper and achieved more quickly, and were associated with fewer instances of progression to accelerated or blast phases in patients with newly diagnosed CML-CP.[7-10]

Nilotinib and dasatinib are well absorbed orally, with 31% and 19% bioavailability, respectively, and are mainly metabolized by the

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liver through oxidation and hydroxylation by way of CYP3A4 to primarily inactive metabolites excreted to the bile duct.[15,16] Although both drugs are generally well tolerated, both can cause various hematologic and nonhematologic adverse events. In the ENESTnd trial, the common nonhematologic adverse events observed with nilotinib included rash, headache, nausea, alopecia, pruritus, myalgia, fatigue, and vomiting. Common biochemical abnormalities included increased levels of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), amylase, lipase, and creatinine.[6] In the DASISION trial, fluid retention (including pleural effusion), myalgia, nausea, diarrhea, vomiting, rash, headache, and fatigue were observed with dasatinib.[10] Grade 3 or 4 biochemical abnormalities included elevated levels of AST, ALT, total bilirubin, and creatinine.[9]

ENESTnd and DASISION both had strict inclusion criteria that included adequate renal and liver function. However, patients frequently present at the diagnosis of CML with mild to moderate liver or renal dysfunction. Currently no data are available on the safety and efficacy of nilotinib and dasatinib in this patient population. The purpose of the present analysis was to determine the safety and efficacy of nilotinib and dasatinib in patients with CML-CP and pre-existing liver and/or renal dysfunction.

Patients and Methods

Patients

For the present analysis, we included 215 consecutive patients with previously untreated CML-CP who had been enrolled in concomitant phase II clinical trials of dasatinib or nilotinib from May 2005 to October 2012 at the MD Anderson Cancer Center.[4,10] These trials were registered at ClinicalTrials.gov (NCT00254423 and NCT00129740; available at www.clinicaltrials.gov). The starting doses of nilotinib and dasatinib were 400 mg twice daily and 100 mg daily or 50 mg twice daily, respectively. The inclusion criteria of the clinical trials included Philadelphia chromosome-positive or BCR-ABL–positive CML-CP diagnosed within 12 months before enrollment. The CP was defined as $< 15\%$ blasts, $< 20\%$ basophils, and $< 30\%$ blasts and promyelocytes in the blood or bone marrow; no extramedullary disease; and a platelet count $> 100 \times 10^9$/L (unrelated to therapy). The patients were also required to be aged ≥ 15 years, to have an Eastern Cooperative Oncology Group performance status of 0 to 2, and to have a total bilirubin of ≤ 1.5 times the upper limit of normal (ULN), an ALT of ≤ 2.5 times the ULN, and creatinine ≤ 1.5 times the ULN. All patients signed an informed consent form that had been approved by the institutional review board in accordance with the Declaration of Helsinki.

Classification of Renal and Liver Function

Renal function and liver function were classified according to the guidelines from the National Cancer Institute Organ Dysfunction Working Group. The creatinine clearance (CrCl) was estimated using the Modification of Diet in Renal Disease method from the National Kidney Disease Education Program (estimated glomerular filtration rate [GFR] [mL/min/1.73 m^2] = 175 × [serum creatinine]$^{-1.154}$ × [age]$^{-0.203}$ × [0.742 if female] × [1.212 if African American]).[17] Normal renal function was defined as a CrCl of ≥ 60 mL/min; mild renal dysfunction as a CrCl of 40 to 59 mL/min; moderate as a CrCl of 20 to 39 mL/min; and severe renal dysfunction as a CrCl of ≤ 20 mL/min. Normal liver function was defined as a total bilirubin level at the ULN or less and an AST level at the ULN or less. Mild liver dysfunction was defined as a total bilirubin level of ≤ 1.5 times the ULN and an AST level greater than ULN. Moderate liver dysfunction was defined as a total bilirubin level of 1.5 to 3.0 times the ULN and an AST level of any value. Finally, severe liver dysfunction was defined as a total bilirubin level > 3.0 times the ULN and an AST of any value.

Monitoring and Assessment of Response

The hematologic, cytogenetic, and molecular response criteria were defined as described previously.[18,19] In brief, complete hematologic remission was defined as normalization of the bone marrow ($< 5\%$ blasts) and peripheral blood (white blood cell count $< 10 \times 10^9$/L and no peripheral blasts, promyelocytes, or myelocytes) for ≥ 4 weeks. Complete cytogenetic responses (CCyRs) were determined by the absence of Philadelphia chromosome–positive metaphases with ≥ 20 metaphases analyzed. A major molecular response (MMR) and molecular response by a 4.5 log reduction (MR4.5) was defined as a BCR-ABL/ABL ratio of $\leq 0.1\%$ and $\leq 0.0032\%$ on the international scale, respectively.

Survival

The survival duration was measured from the start of nilotinib or dasatinib until death from any cause, and patients who were alive at the end of the study period were censored at the date of the last follow-up visit. Event-free survival (EFS) was calculated from the start of nilotinib or dasatinib to the loss of a complete hematologic response, loss of a major cytogenetic response, transformation to accelerated or blast phase, or death from any cause. Failure-free survival (FFS) was calculated from the start of nilotinib or dasatinib to discontinuation or a switch to another treatment for any reason. Treatment-failure survival (TFS) was calculated from the start of therapy to transformation to accelerated or blast phase or death. For EFS and FFS, patients who discontinued therapy for other reasons (eg, noncompliance, financial issues) or who were lost to follow-up were censored at the date of last treatment. Those patients still receiving either agent at the end of the study period were censored at the date of last follow-up visit. Telephone surveys were conducted to determine whenever possible the reasons the patients had been lost to follow-up.

Statistical Analysis

The primary objective of the present study was to analyze the toxicity profiles and response rates of nilotinib- or dasatinib-treated CML-CP in patients with normal organ function or liver and/or renal dysfunction. The secondary endpoints included the 4-year FFS, TFS, EFS, and overall survival (OS) rates. The Fisher exact test and Mann-Whitney *U* test were used to assess the differences between groups. The main analysis for the primary and secondary endpoints was performed in the intention-to-treat population. The 4-year FFS, TFS, EFS, and OS rates were estimated using the Kaplan-Meier method and analyzed using the log-rank test. All reported *P* values are 2-sided, and *P* values $< .05$ were considered statistically significant. Cox proportional hazards regression for survival was used for univariate (UVA) and multivariate (MVA) analysis. Statistically significant variables on UVA were included in the MVA. All statistical analyses were performed using the SPSS, version 22, software program.