Original Study

Evaluating the Impact of a Switch to Nilotinib on Imatinib-Related Chronic Low-Grade Adverse Events in Patients With CML-CP: The ENRICH Study

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Abstract

Chronic treatment-related adverse events adversely affect quality of life, treatment adherence, and clinical outcomes of many patients taking imatinib. The ENRICH (Exploring Nilotinib to Reduce Imatinib Related Chronic Adverse Events) study evaluated the effect of switching 52 such patients to nilotinib. Within 3 months of switching, improvements in imatinib-related adverse events and quality of life and ongoing achievement and maintenance of molecular and cytogenetic responses were observed.

Background: Many patients with chronic myeloid leukemia in chronic phase experience chronic treatment-related adverse events (AEs) during imatinib therapy. These AEs can impair quality of life and lead to reduced treatment adherence, which is associated with poor clinical outcomes. **Patients and Methods:** In the phase II ENRICH (Exploring Nilotinib to Reduce Imatinib Related Chronic Adverse Events) study (N = 52), the effect of switching patients with imatinib-related chronic low-grade nonhematologic AEs from imatinib to nilotinib was evaluated. **Results:** Three months after switching to nilotinib, 84.6% of the patients had overall improvement in imatinib-related AEs (primary endpoint). Of 210 imatinib-related AEs identified at baseline, 62.9% had resolved within 3 months of switching to nilotinib. Of evaluable patients, most had improvements in overall quality of life after switching to nilotinib. At screening, 65.4% of evaluable patients had a major molecular response (*BCR-ABL1* $\leq$ 0.1% on the International Scale). After switching to nilotinib, the rate of the major molecular response was 76.1% at 3 months and 87.8% at 12 months. Treatment-emergent AEs reported with nilotinib were typically grade 1 or 2; however, some patients developed more serious AEs, and 8 patients discontinued nilotinib because of new or worsening AEs. **Conclusion:** Overall, results from the ENRICH study demonstrated that switching to nilotinib can mitigate imatinib-related chronic low-grade nonhematologic AEs in patients with chronic myeloid leukemia in chronic phase, in conjunction with acceptable safety and achievement of molecular responses. This trial was registered at www.clinicaltrials.gov as NCT00980018.

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Introduction

In patients with newly diagnosed Philadelphia chromosome–positive (Ph^+) chronic myeloid leukemia in chronic phase (CML-CP), chronic mild to moderate imatinib-related adverse events (AEs) can negatively affect patient quality of life (QOL), leading to reduced adherence to therapy,[1-3] which is associated with poor responses

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and poor long-term outcomes.[4-7] Therefore, the proper management of AEs is critical for ensuring optimal outcomes.[1,3,6,8] When treatment interruptions and reduced adherence result from imatinib-related toxicities, switching patients to another tyrosine kinase inhibitor (TKI) can improve tolerability and treatment adherence, thereby optimizing responses.

Nilotinib is more potent and selective than imatinib,[9] has demonstrated superior efficacy compared with imatinib,[10-14] and is associated with a safety profile distinct from that of imatinib.[10-14] Compared with imatinib, the incidence of nausea, vomiting, diarrhea, muscle spasms, and edema is lower with nilotinib, although the incidence of rash, headache, and pruritus is higher with nilotinib.[12] In a subset analysis of 95 patients with CML-CP who discontinued imatinib because of intolerance (>75% for grade 3/4 AEs) and switched to nilotinib, cross-intolerance (defined as the occurrence of the same AE with nilotinib that was associated with intolerance to imatinib) was uncommon.[15] In that study, no patient required nilotinib dose reductions or discontinued nilotinib treatment due to the same AE that had led to imatinib discontinuation.[15] Cardiovascular AEs have been reported to varying degrees with all TKIs approved for treatment of CML[14,16-23] and were reported more frequently with nilotinib than with imatinib in the pivotal trial of frontline nilotinib versus imatinib (ENESTnd).[13,14]

The phase II ENRICH (Exploring Nilotinib to Reduce Imatinib Related Chronic Adverse Events) study was conducted to evaluate whether imatinib-related chronic low-grade nonhematologic AEs could be improved and responses optimized by switching patients from imatinib to nilotinib.

Patients and Methods

ENRICH was a phase II, single-arm, open-label, multicenter, exploratory study to determine the effect of switching to nilotinib on the AE profile of patients with low-grade toxicities associated with imatinib therapy (ClinicalTrials.gov identifier, NCT00980018).

Study Design and Treatments

Adults (aged $\geq$ 18 years) with CML-CP and an Eastern Cooperative Oncology Group performance status of $\leq$ 2 were eligible. The patients had been treated with imatinib (any dose) for $\geq$ 3 months before screening and experienced a Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 nonhematologic AE during imatinib therapy that had persisted for > 2 months or had recurred > 3 times despite best supportive care. The patients were required to have achieved the following efficacy milestones with imatinib therapy: after 3 months, a complete hematologic response (CHR); after 6 months, Ph^+ < 95% ($\geq$ 20 metaphases required for standard bone marrow cytogenetics); after 12 months, Ph^+ < 35%; and after 18 months, Ph^+ 0% or *BCR-ABL1* $\leq$ 0.1% on the International Scale (*BCR-ABL1*^{IS}; documented within 3 months). Patients meeting any of the following criteria were excluded: any grade $\geq$ 3 nonhematologic AE within 30 days of screening; previous accelerated or blast phase; loss of a CHR or cytogenetic response (CyR); previously documented T315I mutation; previous treatment with any TKI other than imatinib; impaired cardiac function (including congenital long QT syndrome or a known family history of long QT syndrome, a history or presence of clinically significant ventricular or atrial tachyarrhythmias, clinically significant resting bradycardia, an inability to monitor the QT interval by electrocardiography, Fridericia-corrected QT > 450 ms on the baseline electrocardiogram, myocardial infarction within 1 year of starting the study drug, or other clinically significant heart disease); impaired gastrointestinal function or gastrointestinal disease that could significantly alter absorption of nilotinib; acute or chronic liver, pancreatic, or renal disease; a history of a significant bleeding disorder; pregnancy or nursing; treatment with a cytochrome P450 3A4 inhibitor; or medication with the potential to prolong the QT interval.

Enrolled patients received nilotinib 300 mg twice daily for 12 cycles (1 cycle = 28 days) during the study. No washout period was required between imatinib and nilotinib treatment. The patients were followed up for safety evaluations for 28 days after the last dose of study drug.

Endpoints and Assessments

Imatinib-related chronic low-grade (grade 1 or 2) nonhematologic AEs, hereafter referred to as imatinib-related AEs, were assessed on days 1 and 15 of cycle 1 and at the end of cycles (EOC) 1, 2, 3, 6, 9, and 12. The primary endpoint of the study was the percentage of patients with overall improvement in imatinib-related AEs at EOC 3 after the switch to nilotinib. Overall improvement was defined as either a decrease in CTCAE grade or resolution of $\geq$ 50% of a patient's imatinib-related AEs. The secondary endpoints included the rate of complete CyR (CCyR; defined as negative fluorescence in situ hybridization [FISH] findings or 0% Ph^+ cells) among patients without CCyR at baseline; the rate of major molecular response (MMR) at EOC 1, 2, 3, 6, 9, and 12; *BCR-ABL1*^{IS} log changes following switch to nilotinib; the time to, and duration of, CCyR and MMR during the study; the time to the first documented and optimal improvement in imatinib-related AEs; and safety.

The time to the first documented improvement of imatinib-related AEs was defined as the interval from the first dose of the study drug until the first documented decrease in CTCAE grade. The time to optimal improvement of imatinib-related AEs was defined as the interval from the first dose of the study drug until a maximum decrease in the sum of the CTCAE grades of the events. AEs with an onset date on or after the date of study drug initiation or that had worsened or recurred during study treatment were included in the analysis of AEs occurring during nilotinib treatment. Serious AEs (SAEs) occurring at any point from the initiation of study drug until 28 days after stopping study participation were also analyzed. Nilotinib dose reductions were required for patients with grade 3/4 AEs concerning white blood cells and platelets and grade 2 to 4 nonhematologic AEs. Discontinuation from the study was required if any toxicity had not resolved after 28 days. AEs were assessed using CTCAE, version 4.0.

The times to CCyR and MMR were defined as the interval from the first dose of the study drug to the first documented CCyR or MMR, respectively. The duration of CCyR was defined as the interval from the first documented CCyR to the date of the first documented loss of CCyR or study termination, whichever was earlier. The duration of MMR was defined similarly. Bone marrow cytogenetic assessment was required at screening if no