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Nilotinib 300 mg BID as frontline treatment of CML: Prospective analysis of the Xpert BCR-ABL Monitor system and significance of 3-month molecular response

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ABSTRACT

Sixty patients with early chronic phase CML (ECPCML) received Nilotinib on a phase II study which included a comparison of the Xpert BCR-ABL Monitor™ PCR system with standardized (IS) *BCR-ABL1* real-time quantitative PCR (RQ-PCR). 88% patients achieved MMR with 45% achieving MR4.5. At 3 months *BCR-ABL1/ABL1* IS >1% and <10% was associated with a lower likelihood of subsequent MR4.5 compared to patients with lower levels ($p = 0.018$). No significant difference was observed between methodologies in identifying MMR. Nilotinib induces high molecular response rates in ECPCML and the Xpert BCR-ABL Monitor™ system merits further investigation in this setting.

1. Introduction

Since the introduction of potent tyrosine kinase inhibitors (TKI) molecular monitoring has become an integral part of the management of chronic myeloid leukemia (CML). However, real-time quantitative PCR (RQ-PCR) analysis of *BCR-ABL1* transcripts is a relatively labor intensive procedure, incorporating numerous pre- and post-analytical phases, all of which are potential sources of variation and require rigorous technical attention [1]. A major improvement in reducing this variation would be to introduce a degree of automation. To this end, a cartridge-based system with minimal pre-analytical stages, Xpert BCR-ABL Monitor™ PCR system, has been developed that allows the rapid and reliable quantitation of *BCR-ABL1* transcripts [2–4]. Previous studies have shown this automated, cartridge-based system to be reproducible when compared to manual techniques but no data have been reported from prospective clinical trials [5,6]. Here we report the results of a prospective phase II study evaluating nilotinib 300 mg twice daily (BID) as initial treatment of early chronic phase CML (ECPCML), which included a comparison of the Xpert BCR-ABL Monitor™ PCR system with internationally standardized (IS) *BCR-ABL1* RQ-PCR (ClinicalTrials.gov NCT00809211). This system was prospectively evaluated for the rapid diagnosis of CML and in the setting of residual disease analysis at the level of MMR and levels below this threshold [7].

In this multicenter study, we confirm the efficacy of nilotinib 300 mg BID previously reported in the frontline setting [8]. In addition, we demonstrate: (1) the prognostic significance of reaching *BCR-ABL1/ABL1* IS < 1% at three months, and (2) the accuracy of the Xpert BCR-ABL Monitor™ in positively predicting transcript results reported using the traditional methodology.

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2. Patients and methods

2.1. Study design

This was an open label, single stage, multicenter non-randomized phase II trial to assess the safety and efficacy of upfront nilotinib 300 mg BID (ClinicalTrials.gov NCT00809211). The study design also allowed for rapid escalation of dose to optimize patient responses at the earliest time-point possible. Briefly, patients failing to achieve *BCR-ABL1*/*ABL*1 IS < 10% within 3 months, CCyR within 6 months or MMR within 12 months, were eligible for dose escalation to 400 mg BID in the absence of toxicity. Patients were treated with continuous cycles of nilotinib (each cycle comprising 28 days of treatment) for 2 years. Patients were withdrawn from study if they met criteria for treatment failure (ELN guidelines) or if they had persistent intolerable toxicities [9,10]. The protocol and study documents were approved by the appropriate Institutional Review Board or Ethics Committee. The study procedures adhered to applicable regulatory requirements, Good Clinical Practice, and the Declaration of Helsinki. Written informed consent was obtained from all patients before any study specific procedure was performed.

2.2. Patient eligibility criteria

Patients with Philadelphia chromosome positive CML within 6 months after diagnosis (early chronic phase) were considered eligible for enrollment. The definition of chronic phase CML has previously been described [8,9]. Diagnosis was determined by conventional cytogenetic analysis of bone marrow. Diagnosis by fluorescence *in situ* hybridization was not permitted, but was allowed for monitoring if cytogenetic analysis was not possible. Additional eligibility criteria included: age ≥ 18 years; ECOG performance status of ≥ 2; adequate renal function (GFR ≥ 30 ml/min) and adequate liver function (bilirubin ≤ 1.5 times upper limit of normal and aspartate aminotransferase/alanine aminotransferase ≤ 2.5 times upper limit of normal). Exclusion criteria: treatment with any CML therapy (including imatinib) for longer than 4 weeks (with the exception of hydroxyurea and/or anagrelide) prior to enrollment on study; previously documented T315I mutations; clinically significant heart disease and impaired cardiac function; pregnancy or breastfeeding; uncontrolled intercurrent illness and a history of viral hepatitis and/or HIV. Any medications with the potential to induce or inhibit the cytochrome P450-3A4 pathway or prolong the QT interval were prohibited.

2.3. Study treatment and dose modification

All patients were enrolled to receive nilotinib 300 mg BID. Inability to tolerate a minimum dose of 200 mg QD of nilotinib required removal from the study. To maximize dose intensity the protocol allowed re-escalation of nilotinib to 300 mg BID following dose reductions due to toxicities, provided that the following criteria were met at least one month after dose reduction: all Grade 2 non-hematologic toxicities had resolved to ≤ Grade 1; all Grade 3 hematologic toxicities had resolved to ≤ Grade 1 or alternatively, all Grade 3 toxicities had resolved to ≤ Grade 2 and were manageable with supportive care.

2.4. Endpoints

The primary endpoint for this study was the achievement of complete cytogenetic response (CCyR) at 6 months. Duration of CCyR, MMR and MR4.5 at 3, 6, 9, 12, 18 and 24 months, toxicity, correlation of *BCR-ABL1* transcripts as recorded by Xpert BCR-ABL Monitor™ *vs. BCR-ABL1* IS RQ-PCR and an assessment of the prevalence of *BCR-ABL1* mutations during therapy were all secondary endpoints.

2.5. Xpert BCR-ABL monitor™ analysis

Serial samples were analyzed with the Xpert BCR-ABL Monitor™ pre-treatment and at subsequent three monthly intervals. Results were compared to a *BCR-ABL1*/*ABL1* RQ-PCR methodology that allowed reporting by IS [11].

2.6. Statistics

The statistical significance of differences in response rates between subgroups was compared using Fisher's exact test (GraphPad software) to calculate two-sided *p* values.

3. Results

3.1. Patient characteristics

Patients with ECPCML whose pertinent demographics are listed in (Table 1) were enrolled between December 2008 and May 2011. Patients were enrolled across 6 participating academic centers in Europe (5 sites) and the United States (1 site). At the time of data cutoff, 18 month follow up data were available in all 60 patients, respectively, with a median follow up of 29 months. At this time 52 patients (87%) remained on study.

3.2. Safety

Nilotinib 300 mg BID was well tolerated (Table 2). Musculoskeletal pains of symptomatic ≥ grade 2 toxicity, were seen in 9/60 patients (15%). Skin rashes were infrequent and generally mild (≤grade 2) with a grade 2 skin rash seen in only 10% patients. Biochemical abnormalities were the commonest cause of grade 3 non-hematologic toxicity with a ≥ grade 3 elevation of serum lipase in 15 patients (25%). This was grade 4 in two patients. No patients had evidence of pancreatitis. Grade 3 elevation of ALT was seen in 1 patient only with grade 2 elevation of liver enzymes in 6 (10%) other patients. Hyperglycemia of grade 2 severity was seen in 2 patients (3%) only. Grade 2 and 3 hyperbilirubinemia were seen in 2 patients each (3%). Hematologic toxicity was minimal with thrombocytopenia or neutropenia of grade 3 and 4 severity seen

Table 1
Baseline demographics.

Patient characteristics *n* = 60	
Median age (range) – year	54 (20–77)
Male sex – no. (%)	33 (55)
ECOG performance status – no (%)	
0	41
1	15
2	1
NA	3
Sokal risk group – %	
Low	13
Intermediate	15
High	32
Additional chromosomal abnormalities – no. (%)	4 (7)
Atypical BCR-ABL transcripts – no. (%)	1 (2)
Spleen size > 10 cm below costal margin – no. (%)	7 (12)
Median hemoglobin (range) – g/dl	11.9 (7.2–16.3)
Median platelet count × 10^9/l	370 (105–1715)
Median basophil count × 10^9/l	5 (8)
Median neutrophil count × 10^9/l	4 (6)
Median circulating blast count – × 10^9/l	0.3 (0–22)
Median Ph+ metaphases – no. (range)	20 (2 – 20)