International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

Treatment with Nilotinib 300 Mg Twice Daily in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia Albanian Patients

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Abstract: ***The introduction and the use of nilotinib in the first-line treatment of chronic myeloid leukemia have been based on company-sponsored trials. Independent confirmations are extremely important[1]. We are reporting a study study of nilotinib 300 mg twice daily in 41 chronic myeloid leukemia patients in chronic phase. A deep molecular response was achieved in 45% ($MR^{4.0}$) and 16% ($MR^{4.5}$) of patients at 18 months ; 55% of the enrolled patients achieved a $MR^{4.0}$ at least once, with a sustained $MR^{4.0}$ in 52% of them. With a median observation of 50 months (range 48–60 months), 95 % of patients were still on treatment with nilotinib. The reason for discontinuation was death in 2 patients. An evaluation of metabolic affects showed an increase of total cholesterol and an increase in fasting glucose[2] . This study in Albanian patients with newly diagnosed chronic myeloid leukemia confirms the efficacy of nilotinib 300 mg twice daily(BID) and provides information on the type and incidence of non-hematologic and metabolic adverse events[3].***

Keywords: CML, Albanian patients, nilotinib, chronic phase

1. Introduction

Nilotinib is a second generation BCR-ABL1 tyrosine kinase inhibitor (TKI). It has been approved for the first-line treatment of newly diagnosed, chronic phase (CP) Philadelphia chromosome-positive (Ph+), BCR-ABL1-positive (BCR-ABL1+) chronic myeloid leukemia (CML), following phase 3 prospective randomized trial (ENESTnd) comparing nilotinib to imatinib 400 mg once daily (QD)[4].Several updates of the study, over 6 years, have confirmed the initial findings that nilotinib was superior to imatinib for any degree of molecular response, and for the rapidity of the response[5].The progression-free survival (PFS) was reported to be marginally improved and no difference in overall survival (OS) was detectable. In the ENESTnd trial, two different nilotinib doses were tested, namely 300 mg twice daily (BID) and 400 mg BID [6]. The 300 mg BID dose was selected for approval because it was reported to be as effective as, but less toxic than, the 400 mg BID dose[4].

This concern was by other independent studies, for the most part retrospective and mainly in second-line treatment, reporting a significant incidence of cardiovascular adverse events (CVAEs) during nilotinib treatment. With a minimum observation of 24 months, the molecular response rates in a second single-arm company-sponsored study of nilotinib 300 mg BID, the ENEST1st trial, were even higher compared to the ENESTnd results, with consistent safety data[7] There are no independent, investigator-sponsored studies of the drug in first-line treatment, with the exception of the two small pilot studies that were performed prior to the approval of nilotinib in first-line treatment, at the dose registered for second-line treatment (400 mg bid).When the 300 mg BID dose became the standard in first-line therapy. Since all patients have now been followed for a minimum of 4 years, we report the results of the main analysis of response and adverse events (AEs)[8].

2. Methods

A single-arm study of nilotinib, 300 mg BID was applied in adult patients[9] . Pre-treatment with imatinib for up to 30 days was permitted. The primary endpoint was the rate of EMR at 3 months[10]. The cut-off date for this analysis was September 15.2017.

The detection of a Ph chromosome and/or a *BCR-ABL1* fusion gene associated with consistent morphologic features were required to confirm the CML diagnosis and the chronic (CP), accelerated (AP) or blast disease phase (BP) were defined according to current ELN criteria.[10] Risk scores were calculated according to Sokal,[171819]formulations. The molecular response (MR) was assessed by peripheral blood RT-PCR, according to the International Scale (IS). Definitions: early molecular response (EMR), BCR-ABL1 transcript ≤ 10% at 3 months; major molecular response (MMR or $MR^{3.0}$), BCR-ABL1 transcript ≤ 0.1%; $MR^{4.0}$ and $MR^{4.5}$, BCR-ABL1 transcript ≤ 0.01%, and ≤ 0.0032%, respectively, in samples with > 10,000, and > 32,000 ABL1 copies, respectively; sustained $MR^{4.0}$ or $MR^{4.5}$, stable response for > 1 year with > 3 evaluable tests. Molecular tests were performed every 6 months. The cytogenetic response was assessed by chromosome banding analysis at 3, 6 and 12 months; if there were < 20 available metaphases, a fluorescence *in situ* hybridization (FISH) analysis on peripheral blood cells was accepted (complete cytogenetic response, CCyR, ≤1% of BCR-ABL1 positive nuclei, > 200 nuclei analyzed). OS, PFS, and event-free survival were calculated from treatment start until death (OS), until death or progression to AP or BP (PFS), or until death, progression to AP or BP. Probabilities of OS, PFS and EFS were calculated using the Kaplan-Meier method.[11]

The time to response was calculated from treatment start until the first achievement of the response. The cumulative probability of response was calculated taking into

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consideration the presence of competing risks (failure, progression or death[12]).

The AEs were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). Lipid modifications were graded according to adapted American Association of Clinical Endocrinologists (AACE) criteria, and glucose abnormalities according to adapted American Diabetes Association (ADA) criteria[13].

3. Results

Baseline characteristics

Forty one patients were enrolled between June 2011 and November 2012 at Hematology clinic in University Hospital Center "Mother Teresa" in Tirana, Albania. The median age was 47.59years. Sixty-eight percent were males. High risk patients were 21% according to Sokal risk score.

Patient disposition

The median follow-up was 50 months (range 48-60 months). Overall, 97% of patients were still on nilotinib , mainly at the initial 300 mg BID dose. Two of these patients progressed to AP or BP after 6 and 19 months, respectively; and passed away after that.

Responses and outcome

The 3-month EMR was achieved in 91.6 % of patients (ITT). At 24 months, according to the ITT principle, 65% of patients were in MMR, 46% were in $MR^{4.0}$, and 17% were in $MR^{4.5}$. Overall 58% achieved a $MR^{4.5}$ at least once and 52% achieved a sustained $MR^{4.0}$; The duration of observation is still too short for a detailed analysis of the stability of deep molecular response[14] .

Safety

A grade 3–4 thrombocytopenia and neutropenia were recorded in 10% and 11 % of patients[15]. Hematologic AEs caused early permanent treatment discontinuation in 2 patients. Twenty-five AEs listed under a comprehensive definition of cardiovascular AEs (CVAEs) were reported in 2 patients: arterial thrombosis,); venous thrombosis, arrhythmias, 3 events (2 atrial fibrillations, 1 atrial-ventricular blockade); congestive heart failure[15]. The treatment was temporarily discontinuation. Among the other non-hematologic and non-cardiovascular AEs, only fatigue (14% grade 1–2 and 1% grade 3), bone and muscle and joint pain (22% grade 1–2 and 1% grade 3), and skin rash (23% grade 1–2 and 1% grade 3) were reported in more than 10% of patients. Grade 3–4 laboratory abnormalities were as follows: grade 3 transaminase increase 2% (permanent treatment discontinuation, 1 case), grade 3 bilirubin increase 5%, grade 3 and grade 4 lipase increase 12% and 2%, respectively, and grade 3 amylase increase 1% (no pancreatitis)[16].

According to adapted ADA criteria, and considering the maximum grade reached by each patient while on study, 47%, 11%, 5% and 6% of patients experienced a grade 1 (101–125 mg/dl), grade 2 (126–150 mg/dl), grade 3 (151–200 mg/dl) and grade 4 (>200 mg/dl) hyperglycemia, respectively; 29% of patients had an increase of fasting glucose at 1 year, compared to baseline levels (P<0.001). According to adapted ADA criteria, 47% of patients had a grade 1 (5.7–6.4%), 10% a grade 2 (6.5–6.9%), 3% a grade 3 (7–7.9%) and 5% a grade 4 (≥8%) glycated hemoglobin (HbA1c), respectively, (maximum grade reached on our study); no significant increase of glycated hemoglobin has been observed from baseline[17].

4. Discussion

The introduction and the extended clinical use of second generation TKIs is becoming a very important issue in first-line therapy for CML. They offer a treatment choice that must be weighed for short- and long-term efficacy and toxicity, and for cost-efficacy.[18] The information on nilotinib is limited to data coming from two company-sponsored studies, of which one was designed to compare nilotinib and imatinib, and the other to confirm the rate of deep molecular response on nilotinib[19]. There are no data from independent studies. This study is the first study providing company-independent data on the treatment of newly diagnosed CP CML patients with nilotinib 300 mg BID . The study has some limitations. The major limitation is the limited number of patients. The ENESTnd and the ENEST1st trials were reported with a big number of patients

Two major issues are important in the treatment of CML. One issue is the rapidity and the depth of the molecular response. We found that EMR was achieved more frequently than in both ENEST trials [20].

The significance of these differences cannot be assessed because the three studies are different, with different age distribution and proportion of high-risk (Sokal) patients (28% in ENESTnd, 18% in ENEST1st, 21% in this study), with different enrolment criteria and different guidelines for dose reduction or treatment discontinuation[21].

The second major issue is the so-called cardiovascular toxicity, that includes different events, with different physiopathologic mechanisms and different clinical relevant :arterial thrombosis and atrial fibrillation . The incidence, the severity and the consequences of these complications are difficult to assess and to compare, because they may depend on different variables, including not only the patients characteristics, the baseline cardiovascular risk, the prior treatments and the drug dose[22]. But also the definition of the events and importantly, the accuracy of the event reports, that depends on the retrospective or prospective nature of the data collection. When the GIMEMA study was designed, the cardiovascular toxicity was not yet pointed out, apart from QTc prolongation, and the cardiovascular risk at baseline was not routinely assessed. However, the cardiovascular toxicity was revealed as soon as patient enrolment began, so that the identification and the reporting of CVAEs, in facts, became prospective2[3]. However, monitoring, prophylaxis, and the treatment of CVAEs were left to local investigators, because it was not possible to provide guidelines. Several reports indicated a possible metabolic non-target effect of nilotinib, potentially related to CVAEs; importantly, in our study, fasting glucose, glycated hemoglobin and serum lipids were prospectively assessed. Moreover, to evaluate the clinical impact of metabolic effects, we decided to

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classify the abnormalities according to specific criteria, as recommended by ADA and AACE guidelines[24].

In conclusion, this independent study highlights the therapeutic efficacy of nilotinib, confirming the rates, the velocity, and the depth of molecular response; moreover, it confirms that the risk of cardiovascular toxicity, including several different events, is higher in patients with high cardiovascular risk, requiring specific measures of prophylaxis and monitoring[25].

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