Permanent Bilateral Sensorineural Hearing Loss in a Patient Treated with Nilotinib for Chronic Myeloid Leukemia: A Case Report

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ABSTRACT

Introduction of tyrosine kinase inhibitors was a great milestone towards treatment of Chronic Myeloid Leukemia (CML). Increment in specificity for inhibition of tyrosine kinase enzyme in leukemic cells led to the development of new BCR-ABL fusion protein inhibitors. The anticipation of improved efficacy of drugs and decreased side effects profile was met with encouraging response when Nilotinib as a next step to Imatinib was introduced. However, side effects did occur with nilotinib. Here is a case report of a patient with CML, treated with nilotinib, who later developed an undescribed side effect of permanent sensorineural hearing loss. We could not find any literature support regarding occurrence of this side effect with very potent drug nilotinib. We have to bear in mind that the fantasy of superior specificity and efficacy of nilotinib as compared to imatinib could not prevent it from causing a side effect that had already been described in literature for imatinib.

Keywords: Tyrosine Kinase Inhibitors; Chronic Myeloid Leukemia; Sensorineural Hearing Loss; Nilotinib

INTRODUCTION

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by over activity of tyrosine kinase: a BCR-ABL fusion gene product [1]. This gene is produced by translocation between chromosomes 9 and 22 resulting in the formation of Philadelphia chromosome [2]. The clinical manifestation of this disorder is increased and unregulated clonal proliferation of myeloid stem cells in the bone marrow, resulting in accumulation of mature granulocytes in both bone marrow and blood. The disease encompasses three different phases: chronic phase, accelerated phase and blast crisis. One phase can progress into other without potent treatment [3]. Eighty five percent of patients at the time of diagnosis suffer from chronic phase. Blast crisis is on the other end of spectrum with the clinical expression as acute leukemia, hence high mortality. Survival without appropriate treatment is 3-5 years [4].

The drive to improve the quality and expectancy of life in patients with CML led to the development of revolutionary drugs: tyrosine kinase (TK) inhibitors. First to be introduced was imatinib. Treatment with imatinib led to cytogenetic response in up to 75% of patients. This wonder drug helped people to have hope of normal expectancy of life [5]. It had to be given indefinitely for continued effect. To overcome the resistance and intolerance to imatinib, two new novel drugs were introduced: desatinib and nilotinib [6]. Later, Food and Drug Administration (FDA) approved them as first line treatment for CML in 2010 because of specificity of action against BCR-ABL gene product [7].

Nilotinib, marketed with the name of Tasigna, gained popularity because of its effective role in producing better molecular and cytologic response in patients with CML than first generation TK inhibitors [8]. Many side effects had been described for Tasigna, like QT interval prolongation, myelosuppression, cardiac and vascular occlusive disease, pancreatitis, hepatotoxicity, drug interactions and pleural effusion [9]. But we are going to describe a rare side effect associated with Nilotinib that has not been quoted before. Our patient developed permanent sensorineural hearing loss after few months of treatment with Tasigna. Rarely, have case reports of hearing loss been described with

TK inhibitors, and that too only with the use of imatinib [10]

CASE REPORT

32 year old male was diagnosed with CML when he presented with weight loss, sweats, splenomegaly for 6 months and an abscess in left calf postero-medially for 2 weeks. His laboratory findings at the time of diagnosis are given in table 1.

He was started on hydroxyurea for his extremely high total leucocytes count while awaiting approval of nilotinib (Tasigna) by the Government. One month after the diagnosis, he was put on 300 mg of nilotinib-bid, for his chronic phase of CML. He was monitored for side effects of nilotinib with ECG, complete blood counts, liver function tests and physical examination at regular intervals during treatment. Three months later, he presented with complaints of vertigo, vomiting and tinnitus when his Computer topography (CT) brain scan was done, that turned out to be normal. He was sent home on follow up and symptomatic treatment. One month later, he developed progressive hearing impairment which was significant at the time of consultation with his oncologist. His ear examination was normal. His tympanometery (PTA) showed bilateral profound sensorineural hearing loss.

His treatment was withheld and he was put on 60 mg of prednisolone for a week but his hearing did not improve. Instead, it deteriorated to complete hearing loss bilaterally. On the other hand, his lab parameters had shown encouraging response to the treatment with nilotinib, with decreased granulocytes cell counts and improved hemoglobin. After 3 weeks of cessation of treatment, patient's hearing did not improve. Considering the hearing loss permanent and good response to treatment with nilotinib, resumption of treatment was discussed with the patient and hence, drug restarted after his consent. Nilotinib was reintroduced at 400mg once daily dose and then gradually increased back to 300mg twice a day.

DISCUSSION

FDA approved nilotinib (Tasinga), is a first line of treatment for CML patients in chronic phase due to specificity of Nilotinib for TK activity in leukemic cells. Later, the development of numerous side effects led to the speculation of activity of nilotinib against other TKs as well

Table 1: Laboratory profile of patient at the time of diagnosis

Lab tests	Reports
Complete blood picture	Hemoglobin: 5.9 gm/dl TLC: 557190/mm^3 Differential: Polymorphs: 60% Lymphocytes: 00% Monocytes: 00% Eosinophils: 00% Myelocytes: 21% Metamyelocytes: 05% Basophils: 00% Blasts: 14% Platelets: 140000/mm^3
Peripheral blood picture	Anisocytosis +++, poikilocytosis++, hypochromia+, microcytosis+, macrocytosis+
Bone marrow biopsy	CML in chronic phase
PCR for BCR-ABL Tyrosin Kinase	Positive
Ultrasound abdomen	Massive splenomegaly 30*9cm Hepatomegaly-18cm Small sub centimeter mesenteric lymph nodes
SGPT	21 U/l
LDH	2566 U/l (Normal: <480 U/l)

[11]. Development of pleural effusion in a patient was probably related to its action against PDGFRβ inhibition just like Desatinib which resulted in pleural effusion in 7-35% of patients by inhibiting PDGFRβ enzyme [12]. Several types of TKs, including TK B and TK C, are expressed on mammalian primary auditory neurons [13]. Occurrence of permanent sensorineural hearing loss in a patient treated with imatinib was related to mutations in c-Kit, an intended molecular target for imatinib in the treatment of Gastrointestinal Stromal cell tumour (GIST), that also caused auditory defects in mice. Pharmacological inhibition of c-Kit might negatively affect hearing [14]. We can rightly think of inhibition of c-kit by nilotinib in the pathogenesis of this rare side effect. The side effects related to labyrinth in various clinical trials secondary to nilotinib were mild hearing impairment, tinnitus, vertigo. Our patient developed these similar symptoms on his initial presentation and was managed symptomatically. None of the patients in those case reports went on to develop permanent hearing loss. There is no recommended management yet for this unforeseen side effect of nilotinib. Though Petit C et al recommended treatment should be discontinued when such case was developed secondary to imatinib [14]. Seeing the encoura-

-ging hematological and cytological response in our patient we withheld treatment as well. However, after finding no improvement in hearing loss, treatment was restarted with benefit versus loss governing our decision. Though we need to be more cautious as physicians the next time we see a patient developing hearing complaints, bearing this complication in mind. We need to educate our patients about these side effects and to timely report them to the physician!

Nilotinib, despite of proposed specificity for TK enzyme in leukemic cells, is not deprived of the side effects through its action on other kinases. This lack of specificity might make it act like imatinib. We have to manage by probably stopping treatment, if clinically possible, for preventing permanent hearing loss in any patient presenting with hearing impairment while on treatment with nilotinib for CML. Further cases need to be reported to FDA. We also need to probe the exact pathogenesis of this side effect of nilotinib, as speculated by us and for the development of recommendations for management of such side effects.

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