Audio Vestibular Status in CML Patients on Imatinib Mesylate with Review of Literature

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Abstract Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm occasionally presenting with features of leukostasis as primary symptoms. Hearing loss is occasionally reported in CML patients. Further whether Imatinib mesylate has any effect on vestibular functions is not known. We conducted a preliminary study to assess hearing pattern in patients with CML on long term TKI therapy. This is a single center, cross sectional study from northern-India. Patients of CML who were on regular Tyrosine kinase inhibitors (TKI) therapy for at least 6 months underwent audiovestibular evaluation. A total of 44 CML patients on TKI therapy were assessed over a period of 6 months. The median age of the patients was 41 years, the mean duration of TKI therapy was 36 months. Four patients were found to have otological disorder clinically. On pure tone audiometry of 88 ears normal hearing pattern were found with at low and mid frequencies. There was a down sloping type of curve at higher frequencies in PTA in most of the patients. Cold caloric tests in 42 patients were found as equal response in both ears. We conclude from this preliminary study that there are no audio vestibular dysfunctions amongst patients of CML on TKI. It's a negative study wherein we have ruled out any auditory deficits secondary to Imatinib therapy. Further studies are required to evaluate the audiometric profile in CML patients before Imatinib therapy and

to be compared with the patients already on Imatinib in a large cohort.

Keywords CML · Audiovestibular · Imatinib · TKI · Audiometry

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative monoclonal syndrome of the primitive hematopoietic stem cell, manifested by hyperplasia of hematopoietic tissue, particularly of granulocytic lineage [1]. It is characterised by Philadelphia chromosome translocation, t(9; 22) (q34; p11), resulting in the generation of aberrant bcr/abl transcripts. The abnormal protein produced, causes uncontrolled production of myeloid cells in the bone marrow. These cells crowd out other normal haematopoietic cells, spill over into peripheral blood, infiltrate organs and cause various presenting symptoms of CML [2]. The disease is characterized clinically by myeloid hyperplasia, leucocytosis with basophilia, and splenomegaly. Since 1999, Imatinib mesylate (IM) and later second generation tyrosine kinase inhibitors (TKI) have become the treatment of choice for newly diagnosed patients of CML. With widespread availability of TKI, CML has truly become chronic disease and focus is on long-term complications of TKI.

Deafness in leukemia was first described by Donne in 1844 [3]. Vidal in 1856 observed the relationship between leukemia and deafness by recognizing the external/middle ear involvement [4]. Politzer was the first to report the involvement of inner ear when he histologically studied the temporal bones of a patient having deafness associated with CML [5].

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There are very few case reports [6–11] suggesting ear symptoms associated with CML. There is a controversy on the cause of dysfunction being either from CML disease per se or from the TKI therapy. To the best of our knowledge, no large study has been done so far regarding the otological profile in patients of CML. We evaluated the audiological profile in patients of CML who were on IM and had well controlled disease.

Aim of the Study

To assess the audiological and vestibular functions in patients of CML on regular IM therapy.

Patients and Methods

This is a single center, cross sectional study from North India. We included successively diagnosed patients of CML presenting to Hematology Clinic of Post Graduate Institute of Medical Education and Research, Chandigarh. *Inclusion criteria* included: (a) diagnosis of CML based on ELN guidelines (either bcr/abl or Ph chromosome positivity), (b) of both sexes, (c) age > 12 years (d) started on IM as first line agent for CML (e) compliance ensured. (f) At least 6 months of regular and compliant Imatinib therapy. *Exclusion criteria* included: (a) Any past history of suggestive/proven ENT problems (b) any history of therapy for ear problems in the past. (c) Any history of non-compliance to TKI or alternative form of therapy for CML (d) age > 65 years (owing to higher chances of age related presbycusis).

All patients were started on Imatinib 400 mg/d as first line therapy. All patients were on regular follow up from hematology clinic with compliance ensured. At the time of study, there were no patients on second line TKI (Nilotinib, Dasatinib).

Hematological Evaluation

As part of the study protocol, patients underwent complete examination and blood investigations including haemogram, total/differential leucocytic count (TLC, DLC), RBC count and hematocrit. All patients underwent bone marrow examination and CML diagnosis was made by demonstration of Philadelphia chromosome (Ph chromosome) on cytogenetics or demonstration of BCR ABL by PCR. Patient also underwent evaluation for remission status either by cytogenetic studies (percentage Ph positivity) or molecular studies (bcr/abl transcript levels).

Otological Assessment

All diagnosed CML patients were enquired at baseline for any history of ENT disorders as part of detailed history taking and clinical evaluation at time of diagnosis and starting IM. Study participants were referred to outpatient department of Otolaryngology for otological assessment after a minimum 6 months regular therapy with IM. Evaluation included history of any ear symptoms, clinical examination and battery of audiological/vestibular tests. Audiological test battery included pure tone audiometry (PTA) with high frequency till 16 kHz, speech reception thresholds (SRT), speech discrimination scores (SDS) and brain stem evoked response audiometry (ABR). Vestibular evaluation included cold caloric tests (CCT). Patients having features suggestive of neurological (retrocochlear) findings were planned to undergo radiological evaluation like magnetic resonance imaging (MRI) to rule out other differential diagnoses.

SPSS version 16.0 was used for statistical analysis. Significance was considered for $p < 0.05$.

Observation and Results

A total of 53 patients consented for the study, of which 09 patients were excluded (Fig. 1—Consort diagram). There were 21 (47 %) females and 23 (53 %) males. The median age of study population was 41 years (15–65 years). The median hemoglobin was 11.2 gm/dL (7–14.9; 95 % CI 0631). The median TLC was 6600/ μ L (2600–232,300; 95 % CI 14,287). All the patients were in chronic phase except two patients who were in accelerated phase at the time of otological evaluation. Median platelets count was 223,500/ μ L (57,000–1,950,000; 95 % CI 113,675). All patients at the time of study were on IM, the median duration of 36 months (6–120; 95 % CI 8.85). The best remission response was CCyR in all 44 patients (molecular remission status available in only 27 patients of whom 24 patients had achieved MMR).

All patients had undergone a detailed clinical history and examination related to ears. None of the patients had history of tinnitus or vertigo. Four patients were found to have otological disorder clinically. Two female patients (patient number 4, 8; aged 24, 28 years respectively) had itching and blockage in both ears diagnosed as bilateral secretory otitis media with no hearing loss. Third patient (patient number 24), 32 years old female, had central perforation in right tympanic membrane with 40 db conductive hearing loss and SRT in right ear was 35 db. Fourth patient, 41 year old male patient had non active chronic suppurative otitis media with mixed hearing loss both ears

Fig. 1 Consort diagram **Fig. 2** Mean frequency threshold levels on pure tone audiometry (PTA) in both ears

with air conduction (AC) of 30 db and bone conduction (BC) of 25 db in right ear and AC of 40 db and BC of 35 db hearing loss in left ear and SRT of 28 and 35 db in right and left ear respectively.

There was a down sloping type of curve at higher frequencies in PTA in most of the patients (Fig. 2). The mean thresholds in lower speech frequencies (250, 500 and 1000 Hz) were 14 db in right ear and 15 db in left ear. The mean thresholds at mid frequencies (2, 4 and 8 kHz) were 21 db in right ear and 24 db in left ear. The mean thresholds were 38, 47, 70 and 80 db in the right ear and 43, 55, 70 and 80 db in the left ear at higher frequencies of 10, 12, 14 and 16 kHz respectively. Mean SRT in right ear was 17 and 18 db in left ear. Mean SDS in right ear was 98 and 100 % for left ear. Tone decay was normal in both ears. Mean ABR revealed normal I–III and I–V interpeak

latencies and normal amplitude of wave I, III and V and no abnormality was found in other waves. Cold caloric test (CCT) was found normal and equal in both ears in 42 patients. Cold air caloric test was done in two patients with perforated drums and found normal.

Discussion

Otological Complications in Leukemia

Varied organ manifestations of leukemia have been described in literature for a long time; Deafness in leukemia was first described by Donne in 1844 [3]. Vidal in 1856 observed the relationship between leukemia and deafness by recognizing the external/middle ear involvement [12].

Politzer was the first to identify that leukemic infiltration of inner ear was responsible for the rare complication of sensorineural hearing loss associated with these diseases [13]. In 1945, Druss published aural complications in 16.8 % of leukemia patients including acute otitis media, middle ear infiltration and inner ear hemorrhage [14]. Otological manifestations in CML can be with either because of CML itself or associated with long term TKI therapy. There is published literature to support both the theories. There has been no large study to prove or disprove either of the facts. The intent of our study was to see the effect of TKI therapy on otological manifestations.

CML Disease per se Causing Otological Manifestations

CML has been associated with varied otological symptoms in the past. Most of the available published literature is only in the form of isolated case reports (Table 1).

Proposed Etiologies of CML Induced Hearing Loss

Proposed etiologies include hyperleukocytosis, leukemic infiltration and infection [15, 16]. The inner ear is supplied by the labyrinthine artery (a branch of the anterior inferior cerebellar artery), which has small caliber and its tortuosity predispose it to the effects of hyperviscosity [8]. Hyperviscosity syndrome per se, is responsible for various neurological signs and symptoms attributable to increased blood viscosity [17]. It has been presumed that the abnormally elevated cytocrit causes partial occlusion of vessel (an end artery) supplying the cochlea causing ischemia of the cochlea, resulting in hearing loss. These proposed theories need to be validated in future studies (Table 2).

Imatinib and Otological Complications

There are only three reported human cases in literature of Imatinib induced hearing loss. Of these the first reported case

Table 1 Published literature of cases of CML associated hearing loss

Author	Year of publication	Type of hearing loss	Progression with treatment	Phase of CML (CP/AP/BC)	Type of treatment
Pochedly et al.	1969	U/L SNHL	Not improved	CP	Busulphan
Genden et al.	1995	B/L SNHL	Not improved	CP	Hydroxyurea
Resend et al.	2000	B/L CHL	Improved	CP	Leukapheresis, hydroxyurea
Sung Won Chae et al.	2002	U/L SNHL	Improved	CP	Hydroxyurea, interferon α , leukapheresis
Yao Chung et al.	2004	U/L SNHL	Not improved	CP	Hydroxyurea, interferon α
Tsai et al. [16]	2004	B/L SNHL	Patient died	CP	Hydroxyurea, interferon α , cytarabine
Naithani et al.	2005	B/L SNHL	Audiological improvement	CP	Hydroxyurea
Acar et al.	2007	U/L progressive SNHL	Not improved	CP	Hydroxyurea, Imatinib, intratympanic steroid
Kayhan et al. [8]	2009	B/L SNHL	Not improved	CP	Hydroxyurea, Imatinib, oral steroid
Janssen et al. [17]	2009	B/L SNHL	Not improved	BC (Lymphoid in CNS)	Intrathecal cytarabine
Gokce et al. [18]	2010	U/L SNHL	Improved	CP	Hydroxyurea, intrathecal methotrexate and prednisolone
Kapoor et al. [19]	2013	B/L SNHL	Not improved	CP	Hydroxyurea, Nilotinib
Ejele et al. [20]	2013	B/L SNHL	Partial improvement	CP	Hydroxyurea, Imatinib

Table 2 Future directions of research

Audiological profile amongst newly diagnosed patients with baseline TLC $> 2 \times 10^6/\mu\text{L}$
Audiological profile in patients with proven hyperviscosity syndrome (either with established clinical manifestations such as—cerebral/pulmonary leucostasis and priapism or laboratory evidence of hyperviscosity)
Measurement of blood viscosity in patients with hearing deficit to identify the role of the viscosity in the development of hearing loss

was a 19 year old male with sudden onset bilateral high frequency hearing loss after starting Imatinib (5 days post Imatinib), but he had no improvement in the audiological profile after discontinuing Imatinib [18]. Second patient, a 51 year old male, developed progressive hearing loss while on long term Imatinib therapy but he also simultaneously had lymphoid blast crisis [19]. Thus it is difficult to implicate Imatinib in this case. Thirdly, a 54 year old female patient who was prescribed Imatinib for nephrogenic systemic fibrosis and developed bilateral hearing loss 8 days after starting Imatinib therapy [20]. On discontinuation of the drug, she had an improvement in the hearing acuity. These authors suggested strict vigilance and close monitoring for early signs/symptoms of hearing loss. Their suggestion also include further studies regarding effect of TK inhibition on inner ear and Imatinib-related ototoxicity to clarify the relationship between molecular-target chemotherapeutic agents, such as Imatinib, and hearing loss. This formed the basis of our study. No large cohort study has been done so far to see the incidence of hearing loss and other otological symptoms associated with TKI therapy. In this study, we tried to evaluate the audiometric profile in patients of CML on long term Imatinib therapy. We found that patients have near normal hearing at lower and mid speech frequencies while in higher frequencies they were found to have sensorineural type of hearing loss. This hearing loss at higher frequencies is same as that for the normal population. There was no effect on the vestibular function.

Proposed Mechanisms of Imatinib Induced Hearing Loss

Although TKIs are considered to be highly selective; they can cause adverse effects through both non-target/target tyrosine kinases and other alternate signaling pathways. Multiple types of TKs, (particularly Tyrosine kinase B and Tyrosine kinase C), are expressed on mammalian primary auditory neurons [21]. Mice studies have suggested auditory defects secondary to mutations in c-Kit, a molecular target for Imatinib in treatment of gastrointestinal stromal tumors [22]; thus pharmacologic inhibition of this molecular target through Imatinib might negatively affect hearing. Our study was a negative study wherein we haven't found any effect of tyrosine kinase administration on hearing acuity.

Conclusion

Hearing loss in CML is a rare occurrence. It could be secondary to disease per se or can be secondary to the therapeutic regimens used to treat the same. We conducted a preliminary study to assess hearing pattern in patients

with CML on long term TKI therapy. It's a negative study wherein we have ruled out any auditory deficits secondary to Imatinib therapy. Further studies are required to evaluate the audiometric profile in CML patients before Imatinib therapy and to be compared with the patients already on Imatinib in a large cohort.

Compliance with Ethical Standards

Conflict of interest None.

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