Sensorineural Hearing Loss following Imatinib (Gleevec) Administration

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A 54-year-old woman with nephrogenic systemic fibrosis (NSF), a debilitating disease in which chronic kidney disease patients develop fibrosis of the skin and other organs after exposure to gadolinium-containing contrast agents, was referred to our institution for bilateral fluctuating hearing loss 1 month after initiating treatment with imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp, East Hanover, New Jersey) for NSF,\textsuperscript{1} which has no known associated otopathology. She experienced bilateral hearing loss within 8 days after starting oral imatinib 400 mg daily. No other new medications or chemotherapeutic agents were given. Her dose was reduced to 200 mg daily, without improvement in her hearing after 2 weeks; accordingly, her dose was restored to 400 mg daily.

Physical examination of her ears was unremarkable, and she had no prior otologic history or symptoms. There was hyperpigmentation of the skin on her forearms and hyperpigmentation, cobblestoning, and tethering of the skin on her legs. There were fixed flexion deformities of both knees, and ankle movement was markedly limited.

Although her skin induration improved dramatically, an audiogram obtained 7 weeks after starting imatinib revealed a bilateral sensorineural hearing loss with pure-tone average (PTA) and word recognition scores (WRS) of 40 dB and 92\% in the right ear (AD) and 42 dB and 90\% in the left ear (AS) (Figure 1). Although imatinib therapy was discontinued 2 weeks later, her hearing loss progressed. An audiogram obtained 7 weeks after the previous study demonstrated a flat bilateral sensorineural hearing loss with PTA and WRS of 60 dB and 44\% AD, as well as 62 dB and 14\% AS (Figure 2). Her hearing loss did not improve after a 5-day course of oral prednisone 60 mg daily. Three months later, she experienced fluctuating hearing loss with partial improvement in WRS, ranging from 44\% to 84\% AD and 14\% to 70\% AS. This study was exempt by the institutional review board of the Massachusetts Eye and Ear Infirmary.

Imatinib is an oral tyrosine kinase (TK) inhibitor that was used initially to treat chronic myelogenous leukemia (CML). Imatinib occupies the active site to which adenosine triphosphate binds and selectively inhibits signaling mediated by c-Abl, c-Kit, and the platelet-derived growth factor receptor (PDGFR), as well as Smad-independent signaling by the transforming growth factor–\(\beta\) receptor. It has been approved by the Food and Drug Administration (FDA) to treat CML associated with the Philadelphia chromosome transformation, myelodysplastic/myeloproliferative diseases associated with PDGFR gene rearrangements, systemic mastocytosis, hypereosinophilic syndrome, dermatofibrosarcoma protuberans, and gastrointestinal stromal tumors (GIST). Imatinib has been credited for converting previously fatal diseases such as CML and GIST into manageable chronic conditions.

Sensorineural hearing loss as a consequence of imatinib administration has been reported in only one other patient: a 19-year-old man with CML who developed sudden-onset bilateral, high-frequency hearing loss 5 days after beginning imatinib treatment.\textsuperscript{2} Despite the discontinuation of imatinib, he recovered no hearing after 2 months. A 51-year-old man with CML treated with imatinib was reported to develop progressive hearing loss followed by other neurologic symptoms.\textsuperscript{3} However, a lymphoid blast crisis within his central nervous system was later discovered, and accordingly, it is likely that his hearing loss was caused by the neoplastic process rather than by imatinib therapy.

Although imatinib is considered to be highly selective, all TK inhibitors can cause adverse effects through their actions on both target and nontarget TKs. For example, imatinib may infrequently

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Figure 1. Audiogram obtained 7 weeks after starting imatinib in a patient who demonstrated a bilateral, moderate sensorineural hearing loss with excellent word recognition scores. Tympanometry was normal.

Figure 2. Seven weeks after the audiogram in Figure 1, the sensorineural hearing loss progressed and word recognition scores dropped substantially. Tympanometry was normal.
cause a cardiomyopathy to develop in treated patients. Several types of TKs, including TrkB and TrkC, are expressed on mammalian primary auditory neurons. Because mutations in c-Kit, an intended molecular target for imatinib in the treatment of GIST, cause auditory defects in mice, pharmacologic inhibition of c-Kit might negatively affect hearing. The substantial drop in WRS observed in our patient, with only partial and transient recovery while off imatinib for 3 months, suggests a cumulative, neurotoxic effect of imatinib on her auditory nerve.

Patients treated with imatinib should be followed closely for early signs and symptoms of hearing loss, and if hearing loss is present, treatment should be discontinued immediately. Clinicians should also report such adverse effects to the FDA, as we have. Further studies of the effect of TK inhibition on the inner ear and vigilance for other cases of imatinib-related ototoxicity are needed to clarify the relationship between molecular-target chemotherapeutic agents, such as imatinib, and hearing loss.

**Author Contributions**

Harrison W. Lin, concept and design, drafting the manuscript, final approval; Daniel S. Roberts, drafting the manuscript, final approval; Jonathan Kay, concept and design, critical revisions, final approval; Konstantina M. Stankovic, concept and design, data acquisition and interpretation, critical revisions, final approval.

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