follow-up are necessary to assess the long-term effects. The radiation dose to the healthy liver is hard to estimate for a single patient, since only beta-images are available after treatment with ^{90}Y, and the pretherapeutic scans have limitations due to particle size and the short half-life of ^{99}Tc.

In summary, hepatic arterial embolization with SIR-Spheres™ of patients with midgut carcinoids harbouring liver metastases seems promising, and may lead to long lasting radiological responses and symptomatic relief. The treatment is usually well tolerated.

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Irreversible ototoxicity associated with the use of erlotinib in a patient with pancreatic cancer

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To the Editor

Erlotinib hydrochloride (Tarceva) is an orally administered, reversible inhibitor of human epidermal growth factor receptor (EGFR) tyrosine kinase. So far the toxicity profile of the agent is considered acceptable. The main drug-related adverse-effects are cutaneous toxicity (acne-like rash) and diarrhea [1]. Auditory side-effects have not been reported as a consequence of therapy with erlotinib.

A 66-year-old woman underwent surgical resection of a pancreatic adenocarcinoma in December 2004. Apart from hypertension, her past medical history was unremarkable. In November 2006 she presented with local disease reccurence, confirmed cytologically by endoscopic ultrasound-guided fine-needle aspiration. She was treated with palliative gemcitabine chemotherapy from November 2006 until May 2007. Following the completion of

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(Received 7 May 2008; accepted 16 May 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802213328

6 cycles of chemotherapy, imaging procedures demonstrated progressive intra-abdominal disease, and new lung and bone metastases. At that time, her performance status was such (Eastern Cooperative Oncology Group Performance Status = 2) that she was not considered for further chemotherapy.

In August 2007 she commenced erlotinib monotherapy (150 mg orally once daily). Approximately half an hour following administration of the first dose, she complained of sudden-onset aural fullness, tinnitus, dizziness and severe bilateral hearing loss, most marked in the right ear. These symptoms subsided partially during the remainder of the day but re-appeared with greater intensity after each dose of erlotinib. She continued the erlotinib treatment for 13 days. During that time, her symptoms progressively deteriorated, with significant impairment of communication ability.

On physical examination, the tympanic membranes were normal and there was no evidence of nystagmus. An audiogram was performed, which demonstrated deafness of the right ear and severe sensorineural loss of the left ear (80 db at 1 kHz). The tympanogram was normal in both ears. Because of the severe hearing loss she was not considered suitable for auditory brainstem response (ABR) testing. Magnetic resonance imaging (MRI) of the brain and the internal auditory canals did not reveal any abnormalities. She was managed using a standard protocol for drug-induced sensorineural hearing loss as used at our institution (University Hospital of Patras, Greece). This regimen consisted of intravenous steroids, vasodilators, procaine and a vitamin B complex. A repeat audiogram after 4 days of this regimen did not demonstrate any subjective or objective hearing improvement. After a further 3 days of this regimen, a repeat audiogram again showed no improvement, and this protocol was discontinued. She continued to deteriorate from progressive pancreatic cancer and died a few weeks later without any improvement in her hearing.

The patient described in this case report developed sudden-onset tinnitus, dizziness, as well as severe, irreversible hearing loss after erlotinib administration. An ear-nose-throat (ENT) examination did not demonstrate any pathology from the head and neck area. Moreover, she had no prior otologic history including surgery, excessive noise exposure, or administration of any known ototoxic drug, and she did not report pre-existing hearing difficulties. In addition, her symptoms developed almost immediately after the first dose of erlotinib and progressively deteriorated with each administration. Thus, it was felt that the irreversible hearing loss was caused by erlotinib. Currently, erlotinib is used mainly in pretreated non-small cell lung cancer (NSCLC) patients and in patients with advanced pancreatic adenocarcinoma. The majority of these patients experience a variety of disease-related symptoms, their clinical condition is often poor, and they usually have a short overall survival. Thus, it is possible that erlotinib-induced, clinically significant hearing impairment, although rare, might not always be reported by patients or their carers.

Although we are not able to provide a definitive explanation of the pathogenesis of erlotinib-induced hearing loss, we believe that it might be related to the role of the human epidermal growth factor receptor (HER) signalling in the inner ear. EGFR and HER 2, 3 and 4 receptors are expressed in both sensory and nonsensory cells within the neonatal and adult mouse inner ear. The expression of the receptors in supporting cells, hair cells, and nonsensory cells suggests that they are potentially involved in the regulation of multiple processes, including survival, synaptic maintenance, and cochlear homeostasis, in addition to a role in proliferation [2]. Transgenic mice in which HER signalling in adult supporting cells was disrupted by expression of a dominant-negative HER receptor, developed severe hearing loss, suggesting that the survival of adult spiral ganglion neurons requires HER receptor signalling in the inner ear [3].

Moreover, EGF and transforming growth factor-alpha (TGF-a) are mitogenic for adult vestibular sensory epithelia [4–6]. The up-regulation of the EGFR and its redistribution within the neonatal rat organ of Corti (OC) following neomycin damage support the earlier observation that growth factors acting through EGFR can induce neonatal mammalian auditory hair cell replacement under culture conditions, after aminoglycoside ototoxic damage [7]. The EGFR receptor is also implicated in the differentiation of several cochlear cell types and in the response of the OC to ototoxic damage in the postnatal rat [8].

In our case, the ototoxicity had an apparent impact on the patient's daily activities and quality of life (QoL). Following the development of this adverse effect, her communication abilities and her mobility were considerably reduced due to the severe hearing loss and the dizziness, respectively. It is widely accepted that QoL constitutes an extremely important parameter in patients with aggressive and highly lethal malignancies and thus, although not life-threatening, the development of severe auditory disability in our patient is considered a serious side effect of the treatment.

Currently, similar cases with respect to the use of erlotinib or other treatments targeting the EGFR

receptor have not been described in the literature. Very recently, sporadic cases of ototoxicity due to different molecular targeted agents such as imatinib or bortezomib have been reported [9,10]. Our case highlights the importance of drug-induced ototoxicity and its impact on quality of life. We propose that, although the association is rare, monitoring of changes in hearing perception should be considered for patients who embark on treatment with erlotinib.

In conclusion, acute-onset aural fullness, tinnitus, dizziness and potentially severe hearing loss could be considered as an additional serious, albeit rare, adverse event of erlotinib therapy. The efficacy of erlotinib in a variety of solid tumours is now well documented and with the increasing use of this agent it is important for physicians to be aware of possible ototoxicity in addition to other well established side effects.

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