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POTENTIAL OTOTOXIC EFFECTS OF DIFFERENT GENERATIONS OF *EGFR* TYROSINE KINASE INHIBITORS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Lung cancer is one of the most frequent malignant tumors, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases. Mutations in the epidermal growth factor receptor (EGFR) gene contribute significantly to NSCLC development. EGFR is key for tumor occurrence and progression. The discovery of tyrosine kinase inhibitors (TKI) targeting EGFR has marked significant progress, offering a more rational and effective therapeutic approach. However, TKIs are not free of side effects. Evidence indicates a potential link between TKI therapy and ototoxicity. Given the chronic nature of the treatment of patients with advanced stages of the disease, even minor toxicity can significantly affect the quality of life. It is essential to inform patients about the potential risk of hearing impairment and to regularly monitor for early signs of ototoxicity, thereby optimizing long-term treatment outcomes for patients.*

The study aimed to *review the existing data on tyrosine kinase inhibitors and their potential ototoxicity, including the main mechanisms of pathogenesis.*

Methods: *The search utilized PubMed, Scopus, Embase, Cochrane Library, Web of Science, Google Scholar, and ClinicalTrials.gov to identify scientific publications on ototoxicity caused by TKIs in NSCLC. The keywords "non-small cell lung cancer," "ototoxicity," "gefitinib," "erlotinib," "afatinib," "dacomitinib," and "osimertinib" were used for the search.*

Results: *EGFR plays an important role in developing, maintaining, and repairing sensory and non-sensory structures of the inner ear. In neonatal models, EGFR is expressed in cochlear cells, including the cortical organ, facilitating regeneration and repair. However, in mature systems, EGFR expression decreases, primarily localized in the spiral ganglion, limiting the regenerative ability of auditory cells. By inhibiting EGFR signaling, cellular proliferation and repair mechanisms are disrupted, damaging the cochlea's hair cells and supporting cells.*

Conclusion: *The prevalence and main molecular mechanisms of ototoxicity caused by TKI remain poorly understood. Further research is needed to clarify dose-dependent effects, genetic predisposition, and potential protective strategies. Knowledge of this adverse effect is necessary to monitor auditory health during EGFR-TKI therapy and to study interventions that mitigate its effects on patients undergoing long-term treatment.*

Keywords: *non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR), tyrosine kinase inhibitor (TKI), ototoxicity.*

Introduction: Cancer remains one of the most prevalent and significant global health challenges. In 2022, the worldwide incidence of cancer reached 19,976,499 new cases, with an age-standardized incidence rate of 196.9 per 100,000 population. During the same period, the total number of cancer-related deaths was reported at 9,743,832. Lung cancer is one of the most frequently diagnosed malignancies among both men and women, which highlights its significant contribution to the global cancer burden [1]. Among these cases, non-small cell lung cancer (NSCLC) accounts for approximately 85% [2].

The treatment of NSCLC is based on a multimodal approach, including chemotherapy, radiation therapy, and targeted therapy, aimed at minimizing adverse effects and improving therapeutic efficacy. Mutations in the epidermal growth factor receptor *(EGFR)* gene contribute significantly to NSCLC development. *EGFR* is key for tumor occurrence and progression. The significance of this genetic alteration is supported by Melosky et al.'s (2022) [3] findings, which revealed a significantly higher prevalence of *EGFR* mutations among Asian populations compared to Western populations. This disparity underscores the necessity of developing population-specific therapeutic strategies. Consequently, given the higher prevalence of *EGFR* mutations in Asian countries, using tyrosine kinase inhibitors (TKIs) appears to be the most rational and effective treatment approach for this patient group.

TKI revolutionized the treatment of NSCLC by providing a highly selective mechanism of action, leading to improved clinical outcomes and reduced systemic toxicity compared to conventional chemotherapy [4]. These inhibitors specifically target aberrant signaling pathways driven by mutations in key oncogenes, including *EGFR* [5], *ALK*, and *ROS1*, essential for tumor proliferation and survival [6]. First-generation TKIs, such as gefitinib and erlo-

tinib, demonstrated substantial efficacy in patients harboring *EGFR* mutations; however, their clinical utility was limited by the emergence of acquired resistance, most notably the *T790M* mutation [7]. Second-generation inhibitors, including afatinib and dacomitinib, irreversibly bind to *EGFR*, overcoming some resistance mechanisms [8]. Third-generation TKIs, such as osimertinib, were specifically designed to target *T790M* mutations and have demonstrated improved central nervous system penetration, further enhancing treatment efficacy [9]. The introduction of TKIs into clinical practice has markedly improved the progression-free and overall survival among patients with NSCLC. This made TKIs the main component of personalized cancer therapy.

Although cancer therapy is essential for improving survival rates, it is often associated with significant adverse effects on various organ systems. One of the most severe complications is cardiotoxicity, which can result in heart failure and arrhythmias, particularly in patients receiving anthracyclines or targeted therapies affecting cardiovascular function [10]. Similarly, neurotoxicity is a prevalent adverse effect, manifesting as cognitive impairments and peripheral neuropathy, which may significantly impact patients' quality of life [11, 12]. In addition to cardiovascular and neurological complications, hepatotoxicity and nephrotoxicity are common consequences of chemotherapy and targeted therapies, potentially leading to liver and kidney dysfunction and further complicating treatment regimens [13, 14]. Moreover, ototoxicity represents another critical adverse effect, often causing irreversible damage to auditory and vestibular functions, communication, and balance [15].

Ototoxicity is a severe adverse effect of cancer therapy that significantly affects patients' quality of life [16]. This toxicity is particularly associated with certain chemotherapeutic agents, including platinum-based drugs such as cisplatin, as well as targeted therapies like TKI, both of which have been shown to cause irreversible damage to the auditory and vestibular systems [16, 17]. The underlying mechanisms of ototoxicity involve the accumulation of toxic metabolites within inner ear cells, increased oxidative stress, and the apoptosis of sensory cells, ultimately leading to progressive hearing loss and balance disorders. Given the increasing life expectancy of cancer patients and the need for prolonged treatment, the long-term impact of ototoxicity has become a critical concern in oncology. Further research is essential to understand this issue and formulate effective preventive strategies. Therefore, the current study evaluated and compared the ototoxic impacts linked to EGFR inhibitors across the first, second, and third generations.

The study aimed to review the existing data on TKIs and their potential ototoxicity, including the main mechanisms of pathogenesis.

Materials and Methods: The search was conducted across four electronic databases: PubMed, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov to identify scientific publications on TKI-induced ototoxicity in NSCLC. The search strategy utilized Medical Subject Headings (MeSH) terms, including «non-small cell lung cancer», «ototoxicity», «gefitinib», «erlotinib», «afatinib», «dacomitiniband», «osimertinib». These terms were combined using Boolean operators (AND, OR) to refine the search results.

Inclusion criteria:

– Type of study: Original research (clinical trials, randomized controlled trials, prospective and retrospective cohort studies, observational studies, descriptions of clinical cases). Systematic reviews and meta-analyses. Clinical trials submitted for registration on ClinicalTrials.gov.

– Language of publication: English and Russian.

– Publication time frame: 2014-2024.

– Publication type: Peer-reviewed articles published in journals indexed in the databases PubMed, Scopus, Web of Science, and Google Scholar; unregistered clinical trials, available on ClinicalTrials.gov.

Exclusion criteria:

– Type of research: Low-quality publications that have not passed the review procedure (for example, conference abstracts, letters to the editor, editorial comments, expert opinions, literature reviews without a systematic approach).

– Publication language: Publications in languages other than English and Russian.

– Publication type: Duplicate publications.

– Reviews, comments, unpublished materials, and gray publications (for example, dissertations, reports).

Thus, 47 out of 741 selected sources were included in this study.

Results: *Molecular Mechanisms of the EGFR Signaling Pathway in Oncogenesis. EGFR* is a critical regulator of cellular proliferation, angiogenesis, apoptosis, and metastasis, making it a key target in oncological research and treatment. *EGFR* is a member of the ErbB receptor family, which also includes HER1 (*EGFR*), HER2 (*ErbB2*), HER3 (*ErbB3*), and HER4 (*ErbB4*), so it shares structural similarities and activation mechanisms with these receptors, collectively influencing various cellular processes [18]. A crucial component of *EGFR*-mediated signaling is the *EREG* gene family on chromosome 4, which plays a significant role in cancer progression by activating proliferative and pro-angiogenic pathways [19]. Under normal physiological conditions, *EGFR* activation triggers a complex intracellular signaling cascade involving pathways such as Ras/Raf/MEK/ERK, PI3K/Akt, PLCγ, JAK/STAT, and Src, which regulate cell growth, survival, migration, and angiogenesis [20]. Dysregulation of these pathways due to aberrant *EGFR* activation is a major driver of tumorigenesis, further underscoring the receptor's role as a crucial therapeutic target in cancer treatment.

The Ras/Raf/mitogen-activated protein kinase (MAPK) signaling cascade is a key regulator of cell proliferation and survival. Upon *EGFR* phosphorylation, adaptor proteins such as Grb2 and Sos are recruited, facilitating the activation of Ras, which serves as a critical intermediary between receptor activation and downstream intracellular signaling pathways [21]. This activation initiates a cascade in which Ras stimulates Raf-1, ultimately leading to the phosphorylation and activation of MAPKs [22]. While MAPK signaling is essential for maintaining normal cellular

functions, its dysregulation can profoundly impact apoptotic regulation. Specifically, persistent activation of extracellular signal-regulated kinase (ERK) inhibits the pro-apoptotic c-Jun N-terminal kinase (JNK) and p38 pathways, thereby disrupting the balance between cell survival and programmed cell death [23]. As a result, excessive MAPK activation suppresses caspase activity, promoting uncontrolled cell survival and facilitating tumor progression. This dysregulation underscores the critical role of MAPK signaling in oncogenesis and highlights its potential as a therapeutic target in cancer treatment.

Another crucial signaling route is the phosphoinositide 3-kinase (PI3K)/Akt pathway, which governs cell growth, survival, and resistance to apoptosis. PI3K, a dimeric enzyme, produces signaling molecules that activate Akt, a key serine/threonine kinase in cellular protection mechanisms [24]. *EGFR*-dependent PI3K activation is primarily mediated through HER3 dimerization, as *EGFR* lacks direct binding sites for PI3K regulatory subunits. Additionally, phospholipase Cγ (PLCγ) interacts with activated *EGFR*, catalyzing the breakdown of phosphatidylinositol 4,5-bisphosphate into inositol triphosphate (IP3) and diacylglycerol (DAG) [25]. This reaction regulates intracellular calcium release and activates protein kinase C (PKC), subsequently influencing MAPK signaling [26]. Signal transducers and activators of transcription (STAT) proteins, particularly STAT3, play a pivotal role in *EGFR*-mediated signaling by regulating key oncogenic processes. Upon activation, STAT proteins form dimers and translocate to the nucleus, modulating gene expression in cell proliferation, survival, and metastasis, thereby contributing to cancer progression [27]. In parallel, the Src kinase pathway is another crucial regulator of *EGFR* signaling, influencing cellular processes such as proliferation, adhesion, migration, and immune responses [28]. Src enhances *EGFR* activation and contributes to resistance against targeted therapies by interacting with alternative receptor pathways, allowing tumor cells to circumvent *EGFR* inhibition [29]. The interplay between STAT, Src, and *EGFR* signaling underscores the intricate nature of oncogenic networks and highlights the need for therapeutic strategies that target multiple pathways to overcome resistance and improve treatment efficacy.

Mechanisms of Action of EGFR Inhibitors of Different Generations. EGFR TKIs are categorized into three generations, each targeting specific *EGFR* mutations and addressing resistance mechanisms. These inhibitors exert their therapeutic effects by competitively binding to the ATP-binding site of the EGF Rkinase domain, thereby preventing the activation of downstream signaling pathways involved in tumor proliferation, survival, and metastasis. First-generation *EGFR*-TKIs function as reversible inhibitors that selectively target tumors harboring activating *EGFR* mutations, particularly exon 19 deletions and the L858R substitution in exon 21 [30]. These inhibitors bind reversibly to the ATP-binding pocket of *EGFR*, effectively suppressing aberrant signaling. However, despite their initial efficacy, their clinical utility is significantly compromised by the emergence of acquired resistance, predominantly driven by the T790M mutation in exon 20. This mutation enhances ATP affinity, thereby reducing the binding efficiency of first-generation TKIs and ultimately leading to treatment failure [31]. The clinical significance of first-generation TKIs was underscored by the regulatory approval of gefitinib by the U.S. Food and Drug Administration (FDA) on July 13, 2015. This approval is specifically applied to patients with metastatic non–small cell lung cancer (NSCLC) whose tumors harbor *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, as confirmed by an FDA-approved diagnostic test [32].

Second-generation *EGFR*-TKIs function as irreversible inhibitors, offering a broader spectrum of inhibition than their first-generation counterparts. These inhibitors covalently bind to a cysteine residue within the ATP-binding domain of *EGFR*, leading to irreversible receptor inhibition. Unlike first-generation TKIs, second-generation inhibitors exhibit expanded activity by targeting multiple receptors within the ErbB family, including *EGFR*, HER2, and HER4, thereby reducing the likelihood of resistance development through alternative pathway activation [33]. However, despite their broader inhibition profile, second-generation TKIs remain ineffective against the T790M mutation, a major resistance mechanism limiting ATP-competitive kinase inhibitors' efficacy. The T790M mutation increases ATP affinity, thereby reducing the binding efficiency of these inhibitors and necessitating the development of third-generation TKIs. Although irreversible inhibitors address resistance by forming covalent bonds with *EGFR*, second-generation TKIs cannot selectively target T790M, making them insufficient in overcoming this specific mutation [34]. The clinical relevance of second-generation TKIs was demonstrated by the FDA approval of afatinib in 2018 for treating rare *EGFR* point mutations. Specifically, afatinib was approved for patients with tumors harboring the S768I, L861Q, and G719X mutations, underscoring the continued refinement of targeted therapies to address diverse *EGFR* mutation profiles [35].

Third-generation *EGFR*-TKIs, irreversible Mutant-Selective Inhibitors, include Osimertinib (AZD9291), Rociletinib (CO-1686), and WZ4002. These inhibitors selectively target both *EGFR*-activating mutations and the T790M resistance mutation, the most common mechanism of acquired resistance. They form an irreversible covalent bond with the ATP-binding site, inhibiting *EGFR* signaling even in resistant tumors. Unlike second-generation inhibitors, they spare wild-type *EGFR*, reducing off-target toxicities such as skin rash and diarrhea. Osimertinib was the first third-generation *EGFR*-TKI to receive regulatory approval from both the FDA and EMA (2015, 2016) for patients with metastatic *EGFR*-mutant NSCLC [36] harboring the T790M mutation [37].

Ototoxicity of EGFR Inhibitors. Mechanisms and Potential Consequences. Unlike traditional chemotherapy, targeted therapy offers a more selective mechanism of action by specifically inhibiting molecular markers, thereby reducing systemic toxicity and minimizing adverse effects [39]. However, despite its improved safety profile, *EGFR* TKIs are associated with various treatment-related toxicities.

Ding et al. (2017) evaluated the risk of adverse effects associated with *EGFR* TKIs, including gefitinib, erlo-

tinib, and afatinib. The study identified diarrhea (53.3%) and rash (66.5%) as the most frequently reported adverse events, affecting more than half of the patients. These toxicities represent the most common treatment-related adverse effects, underscoring the clinical burden of *EGFR*-targeted therapies [40]. The high incidence of cutaneous toxicities, particularly rash, is primarily attributed to the widespread expression of *EGFR* in the skin. Since *EGFR* plays a pivotal role in skin homeostasis and repair, its inhibition disrupts normal cellular processes, leading to dermatologic side effects such as rash and dryness (41). In addition to skin-related toxicities, *EGFR* TKIs have been associated with a range of systemic adverse effects, including fatigue, oral ulcers, constitutional symptoms, nausea, elevated alanine aminotransferase (ALT) levels, dyspnea, and pulmonary toxicity [41].

Table 1 – Mechanisms of Action and Selectivity of Epidermal Growth Factor Receptor *(EGFR)* Tyrosine Kinase Inhibitors (TKI) [38]

EGFR TKI		Selectivity	Mechanism
1 generation	Gefitinib Erlotinib	Reversible *EGFR* inhibitors	*EGFR*
2 generation	Afatinib Dacomitinib Lapatinib	Irreversible inhibitors of *EGFR*, HER2, and HER4	*EGFR*, HER2, HER4
2 generation	Osimertinib Rociletinib	Selective inhibition of mutant *EGFR* (T790M)	*EGFR* (T790M)

The ototoxic effects of *EGFR* inhibitors remain insufficiently studied in the scientific literature. However, several studies indicate a potential association between the use of TKI and the development of sensorineural hearing loss (SNHL), highlighting the need for further investigation. *EGFR* is a transmembrane receptor tyrosine kinase that regulates key cellular functions, including cell proliferation, survival, angiogenesis, and migration. It plays a crucial role in various tissues, including the inner ear, which is involved in auditory processing [42]. The organ of Corti, located within the cochlea, contains mechanosensory hair cells responsible for converting sound vibrations into electrical signals transmitted to the brain. These cells closely interact with sensory neurons, and any disruption in this connection may result in SNHL. Research suggests that *EGFR* signaling is essential for maintaining this interaction, and its dysfunction may contribute to hearing impairment [43].

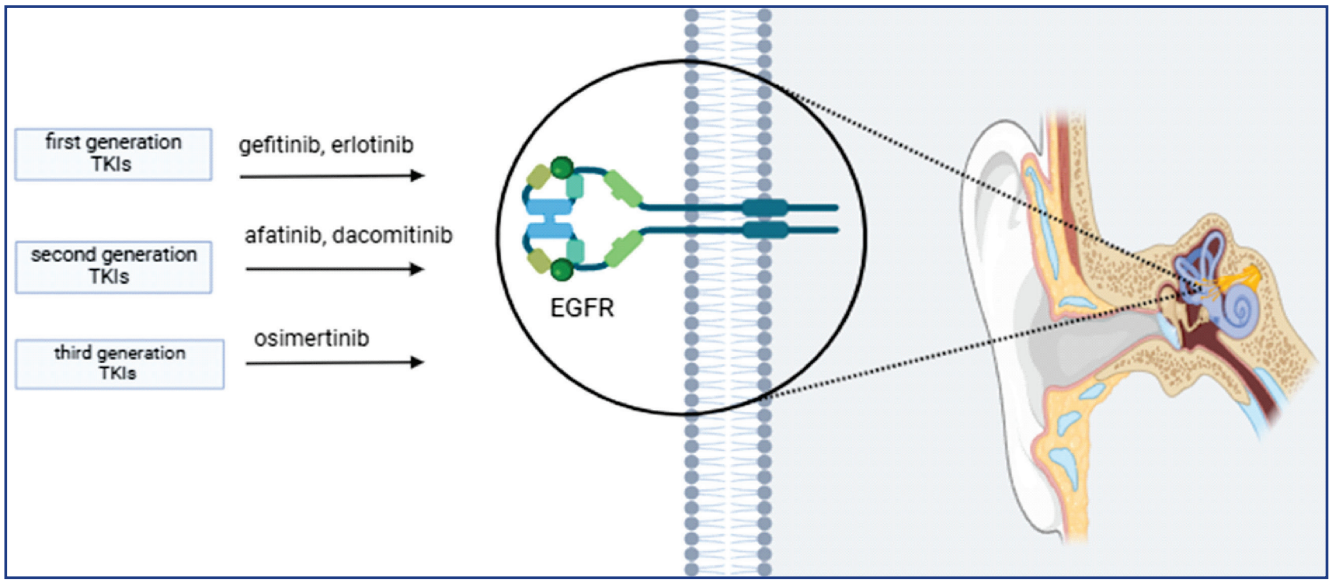

Figure 1 – Targeted Therapy Based on Types of Epidermal Growth Factor Receptor *(EGFR)* Tyrosine Kinase Inhibitors (TKIs)

One of the mechanisms explaining the role of *EGFR* in hearing is its involvement in the proliferation of cochlear-supporting cells. Normally, these cells possess a certain regenerative potential, but in the absence of *EGFR* signaling, they lose their ability to divide and repair damage, thereby limiting the regenerative capacity of the auditory system [44]. Various experimental studies support this hypothesis. For example, a study by Hume et al. (2003) conducted on Swiss Webster mice demonstrated that *EGFR* is expressed in sensory and non-sensory cochlear cells, including the organ of Corti, during early development. In the neonatal period, *EGFR* facilitates the repair of damaged cells; however, its expression declines with age and becomes predominantly restricted to the spiral ganglion. This reduction may explain the limited regenerative ability of the auditory system in adults [45]. Although these sources [44, 45] are over 10 years old, they represent foundational experimental work that has not been contradicted and is still cited in recent literature. These studies were among the first to describe the expression and function of *EGFR* in the cochlea and continue to provide essential mechanistic insight into the limited regenerative capaci-

ty of auditory cells – information that more recent studies often take as a basis for further investigation. These findings support the hypothesis that diminished *EGFR* signaling may contribute to progressive hearing loss. Additional evidence for this hypothesis has been obtained from experimental models. For instance, pharmacological inhibition of *EGFR* in Danio rerio (zebrafish) embryos has been shown to cause auditory dysfunction, underscoring the critical role of this receptor in auditory development and maintenance [46]. A potential link between TKI and hearing impairment has been observed in pharmacovigilance data. An analysis of reports from the FDA Adverse Event Reporting System identified a statistically significant association between the use of capmatinib, a MET TKI, and the development of adverse effects such as hearing loss and dysphagia [47].

Mechanisms of Ototoxicity: EGFR Inhibitors of Different Generations. As noted in the previous sections of this article, ototoxicity is a rare but noteworthy adverse effect associated with *EGFR* TKI. Although research on this phenomenon remains limited, existing studies provide evidence supporting the occurrence of ototoxicity in patients receiving these therapies. This section reviews documented cases and clinical studies investigating the ototoxic effects of *EGFR* TKIs. According to available data, several TKIs have been implicated in hearing impairment, including gefitinib, erlotinib, osimertinib, lapatinib, and canertinib.

First generation-Gefitinib. The ototoxic effects of first-generation *EGFR* TKIs are most commonly reported with gefitinib. For example, Zhu et al. (2023) documented a case of gefitinib-induced ototoxicity in a 51-year-old female patient diagnosed with right-sided bronchogenic adenocarcinoma (T4N3M1c, stage IVB, *EGFR*-mutation positive). The patient developed drug-induced bilateral SNHL and psychiatric disturbances after four months of gefitinib treatment. The patient had no prior history of hearing impairment or deafness before initiating gefitinib therapy. However, hearing loss occurred approximately four months after treatment initiation. Three months after starting treatment, she independently discontinued gefitinib, which resulted in a partial recovery of her auditory function. However, as her underlying malignancy progressed, she experienced worsening cough and wheezing, necessitating hospitalization. Following the deterioration of her condition, gefitinib therapy was resumed. After three days of reinitiation, the patient reported a recurrence and worsening of hearing loss, particularly in the right ear. Moderate to severe bilateral SNHL was confirmed through otoscopic evaluation, audiometric testing, and hearing assessment [43].

In another publication, Timuda et al. (2022) documented a case of a 51-year-old female patient diagnosed with right-sided bronchogenic adenocarcinoma (T4N3M1c, stage IVB, *EGFR* mutation-positive) who developed progressive visual impairment, severe bilateral SNHL, and psychiatric disturbances following 15 months of gefitinib therapy. Magnetic resonance imaging and computed tomography scans of the brain did not reveal evidence of metastatic involvement. Comprehensive audiological assessment, including otoacoustic [17].

In a case reported by Koutras et al. (2008), a 66-year-old female patient underwent surgical resection of pancreatic adenocarcinoma in December 2004 following endoscopic ultrasound-guided fine-needle aspiration. She subsequently received palliative chemotherapy with gemcitabine from November 2006 to May 2007. In August 2007, she initiated monotherapy with erlotinib (150 mg orally once daily). Notably, approximately 30 minutes after the first dose, the patient experienced the sudden onset of ear fullness, tinnitus, dizziness, and profound bilateral hearing loss, with greater severity in the right ear. While these symptoms partially subsided throughout the day, they recurred with increasing intensity following each subsequent dose of erlotinib. Despite the progressive worsening of auditory symptoms, the patient continued erlotinib therapy for 13 days, during which her hearing impairment significantly deteriorated, resulting in substantial communication difficulties. A physical examination revealed normal tympanic membranes with no evidence of nystagmus. The audiometric evaluation confirmed complete hearing loss in the right ear and severe SNHL in the left ear (80 dB at 1 kHz). Tympanometry results were within normal limits for both ears. Standard treatment protocols for drug-induced SNHL were administered; however, no significant improvement in auditory function was observed [42].

Second generation, Canertinib: J. Tang et al. (2015) investigated canertinib ototoxic effects using Danio rerio (zebrafish) and murine models. For an hour, free-swimming zebrafish larvae were exposed to canertinib (0-500 μM). Following exposure, the larvae were fixed, incubated with anti-parvalbumin primary antibodies, and stained with fluorescent secondary antibodies. The number of hair cells in neuromasts was assessed using a Zeiss Axioplan II microscope. In murine studies, two groups were used: a control group (receiving saline) and an experimental group (receiving canertinib at 30 mg/kg/day). Clinical trial dosages included 50, 150, and 450 mg/day, with the highest dose administered in a 14-day cycle followed by a 7-day break. The most common adverse effects in patients were rash and diarrhea. In murine studies, lethality was observed at 120 mg/kg/day doses, whereas 30-60 mg/kg/day doses were well tolerated without significant weight loss. Canertinib at concentrations up to 50 μM did not exhibit noticeable toxicity to zebrafish hair cells; however, at 100 μM ($p=0.28\times10^{-3}$) and 200 μM ($p=0.18\times10^{-10}$), significant hair cell loss was observed. In mice, ABR threshold shifts across five tested frequencies did not show a significant drug effect ($F=2.267$, $p=0.137$), but a significant impact was detected at 40 kHz ($F=5.392$, $p=0.024$). At the end of the experiment, cochlear histological analysis was performed to assess hair cell loss. Canertinib induced a dose-dependent loss of hair cells in the auditory system, confirming its potential ototoxicity [46].

Third generation – Osimertinib. Chee Chean Lim (2022) documented a case of a 72-year-old male diagnosed with stage IV lung adenocarcinoma harboring an exon 19 deletion in the *EGFR* gene [42]. The patient was prescribed oral osimertinib at a dosage of 80 mg once daily. However, six months into treatment, he developed progressive hearing impairment and bilateral tinnitus, prompting referral to an

otolaryngologist. Otoscopic examination revealed no abnormalities, while pure-tone audiometry (PTA) demonstrated moderate-to-severe bilateral SNHL.

Discussion: Our findings reaffirm that *EGFR* is a central regulator of cellular proliferation, apoptosis, migration, and angiogenesis, with its dysregulation playing a pivotal role in oncogenesis [18–20]. As a member of the ErbB receptor family, *EGFR* forms heterodimers with HER2-4, amplifying downstream signaling through MAPK and PI3K/Akt pathways, thus contributing to malignant transformation. These results align with recent literature emphasizing the multifaceted nature of *EGFR*-mediated signaling and the therapeutic challenges posed by pathway redundancy and acquired resistance mechanisms.

The *EREG* gene, located on chromosome 4, plays a particularly critical role, as it encodes an *EGFR* ligand and drives autocrine and paracrine stimulation of tumor proliferation and angiogenesis [19, 25]. Elevated expression of *EREG* has been associated with tumor aggressiveness and poor prognosis in various cancers, including NSCLC, colorectal cancer (CRC), and head and neck squamous cell carcinoma (HNSCC). Emerging evidence suggests that *EREG* contributes to resistance against *EGFR* TKIs, such as erlotinib and gefitinib, through sustained activation of PI3K/Akt and ERK pathways. This creates a state of oncogene addiction in tumor cells, making the *EREG-EGFR* axis a promising target for therapeutic intervention.

The MAPK pathway also plays a central role in *EGFR*-driven oncogenesis. *EGFR*-induced Ras/RAF/ERK signaling activation suppresses JNK/p38-mediated apoptotic responses, thereby enhancing tumor cell survival [21-23]. This is consistent with recent studies highlighting ERK1/2's regulatory influence on cell cycle progression via cyclin D and inhibition of pro-apoptotic cascades. Similarly, PI3K/Akt signaling, often initiated through HER3 dimerization with *EGFR*, supports cellular resistance to stress and apoptosis, underscoring its oncogenic significance [24].

Beyond these classical routes, our analysis underscores the importance of alternative signaling modules, including PLCγ/IP3/DAG–PKC, STAT3, and Src kinases. STAT3, upon activation by *EGFR*, modulates transcriptional programs related to proliferation, survival, and metastasis [27]. Src, in turn, enhances *EGFR* signaling and enables therapeutic escape by activating parallel oncogenic pathways [28, 29]. This complex interplay further illustrates the need for combinatorial therapeutic approaches.

Of particular note are recent efforts to target *EREG* directly. Antibody-drug conjugates (ADCs) and neutralizing antibodies against *EREG* have demonstrated significant antitumor activity in preclinical models. In CRC, demethylation of the *EREG* promoter has been shown to restore sensitivity to cetuximab, suggesting that epigenetic modulation may augment *EGFR*-directed therapies. Additionally, the *EREG/EGFR* axis has been implicated in immune evasion. In HNSCC, glycosylated *EREG* upregulates PD-L1 expression, contributing to an immunosuppressive microenvironment. Inhibitors targeting STT3B-mediated glycosylation of *EREG* are currently under investigation as potential tools to enhance antitumor immunity.

Finally, while current *EGFR*-TKIs such as gefitinib and osimertinib provide clinical benefit in tumors harboring activating *EGFR* mutations, resistance inevitably develops through secondary mutations (T790M, C797S) or bypass signaling. Consequently, therapeutic strategies must evolve to include inhibitors of parallel and downstream effectors, including *EREG* and its associated cascades, to overcome resistance and achieve durable responses.

EGFR-TKIs have a more selective mechanism of action than traditional chemotherapy, allowing for reduced systemic toxicity. However, despite their improved safety profile, there have been reports of rare but clinically significant adverse effects, including ototoxicity. While cutaneous and gastrointestinal toxicities such as rash and diarrhea are well-documented, hearing impairment remains insufficiently studied. Nonetheless, both clinical observations and experimental data suggest a potential association between *EGFR*-TKI therapy and the development of SNHL.

EGFR plays a critical role in various tissues, including the inner ear. It is expressed in cochlear structures such as the organ of Corti, the spiral ganglion, and supporting cells, which are essential for transducing sound vibrations into neural signals. Disruption of *EGFR* signaling may impair the regenerative capacity of supporting cells, resulting in auditory dysfunction. Preclinical studies using zebrafish and murine models have demonstrated that pharmacological inhibition of *EGFR* leads to a dose-dependent loss of hair cells and elevated hearing thresholds. Age-related downregulation of *EGFR* expression in cochlear tissues may also explain the limited regenerative potential of the auditory system in adults.

Clinical case reports further support the ototoxic potential of *EGFR*-TKIs. For instance, a 51-year-old patient developed bilateral SNHL four months after initiating gefitinib therapy. Partial recovery was observed upon discontinuation, but symptoms recurred and worsened following the reintroduction of the drug [17]. In another case, a 72-year-old patient receiving osimertinib developed progressive bilateral hearing loss and tinnitus within six months of treatment, which deteriorated over the following year to severe SNHL [42]. Acute-onset hearing loss has also been reported following the initial dose of erlotinib.

Experimental evidence corroborates these findings. Canertinib exposure in zebrafish resulted in significant hair cell loss in neuromasts, while murine models showed hearing threshold shifts, particularly at high frequencies [46]. Similarly, lapatinib, especially in combination with trastuzumab, induced apoptotic changes in the organ of Corti and the spiral ganglion in rodent models [48].

Although many studies remain limited, existing data indicate that *EGFR*-TKIs may exert ototoxic effects. As patient survival improves with targeted therapies, the clinical relevance of such adverse events becomes increasingly important. Consequently, regular audiological monitoring should be considered, particularly when early symptoms such as tinnitus or aural fullness arise. There is also a pressing need for prospective studies to assess the true incidence of *EGFR*-TKI-induced ototoxicity, elucidate the underlying mechanisms of auditory damage, and explore potential protective strategies.

Conclusion: This study highlights the potential ototoxic effects of various TKIs, including erlotinib, canertinib, and osimertinib, as evidenced by clinical case reports and experimental research. While these targeted therapies are effective in oncology, they may contribute to SNHL through mechanisms that require further investigation. Preclinical studies using zebrafish and murine models demonstrate dose-dependent hair cell toxicity, raising concerns about auditory damage in human patients. Clinical cases further emphasize delayed-onset and progressive SNHL in individuals undergoing TKI therapy, underscoring the importance of early detection and monitoring.

Moreover, physicians should counsel patients receiving *EGFR* TKIs about the potential risk of hearing loss and monitor for early symptoms. Since these patients typically have advanced-stage disease and undergo long-term treatment, even mild toxicities must be managed to maintain their quality of life. Unaddressed hearing loss can lead to communication difficulties, social isolation, and reduced adherence to therapy. A multidisciplinary approach, including comprehensive supportive care, is essential to optimizing treatment tolerability and preserving auditory function in cancer patients.

Supportive care therapy aimed at reducing ototoxicity includes an integrated approach involving oncologists, otorhinolaryngologists, audiologists, pharmacologists, and nurses, covering the following areas. Hearing monitoring (audiological support): initial audiometry before starting tyrosine kinase inhibitor therapy. Regular audiological examinations (tonal audiometry, speech audiometry, otoacoustic emission, registration of auditory evoked potentials) during treatment. Early diagnosis and identification of the first signs of ototoxicity for timely intervention. Pharmacological prophylaxis: prescribing drugs with antioxidant action to reduce oxidative stress in the cochlea of the inner ear. The use of neuroprotective agents can reduce the risk of sensorineural damage.

Rational selection of the therapy regimen: individualization of the treatment regimen considering the risk factors of ototoxicity. Dose adjustment of drugs in case of early symptoms of ototoxicity. In case of severe ototoxicity, it is possible to switch to alternative drugs or adjust dosages.

Patient education and psychological support: informing the patient about possible symptoms of ototoxicity (tinnitus, congestion, dizziness, hearing loss) and the need to inform the doctor promptly. Psychological and social support for the adaptation of patients to possible hearing changes.

Hearing rehabilitation: the use of hearing aids and other technical means of hearing correction with a significant decrease in hearing function. Vestibular rehabilitation for balance disorders and dizziness.

Treatment of concomitant diseases (e.g., diabetes mellitus, cardiovascular diseases) that may increase the risk of ototoxicity.

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АҢДАТПА

EGFR ТИРОЗИНКИНАЗА ИНГИБИТОРЛАРЫНЫҢ ӘРТҮРЛІ БУЫНДАРЫНЫҢ ӘЛЕУЕТТІ ОТОТОКСИКАЛЫҒЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Контрасты Өзектілігі: Өкпенің қатерлі ісігі жиі диагноз қойылған қатерлі ісік. Барлық жағдайлардың ішінде өкпенің ұсақ жасушалы емес қатерлі ісігі (NSCLC) шамамен 85% құрайды. NSCLC дамуының негізгі факторы ісіктің пайда болуы мен дамуында шешуші рөл атқаратын эпидермиялық өсу факторы рецепторы (EGFR) генінің мутациясы болып табылады. EGFR-ге бағытталған тирозинкиназа ингибиторларының (TKI) пайда болуы негұрлым ұтымды және тиімді терапевтік тәсілді ұсына отырып, айтарлықтай прогреске қол жеткізді. Тирозинкиназа ингибиторларының жанама әсерлері жоқ емес. Тирозинкиназа ингибиторлары терапиясы мен отоуыттылық арасындағы ықтимал байланысты көрсететін деректер пайда болады. Аурудың асқынған сатысы бар науқастарды емдеудің созылмалы сипатын ескере отырып, тіпті шамалы уыттылық өмір сапасына айтарлықтай әсер етуі мүмкін. Пациенттерді есту қабілетінің нашарлау қаупі туралы хабардар ету, пациенттерді емдеудің ұзақ мерзімді нәтижелерін оңтайландыру үшін отоуыттылықтың ерте белгілеріне тұрақты мониторинг жүргізу маңызды.*

Зерттеудің мақсаты *– тирозинкиназа ингибиторлары, олардың ықтимал отоуыттылығы, соның ішінде патогенездің негізгі механизмдері туралы бар деректерді зерттеу.*

Әдістері: *NSCLC-де TKI индукцияланған отоуыттылық туралы ғылыми жарияланымдарды анықтау үшін PubMed, Scopus, Embase, Cochrane Library, Web of Science, Google Scholar және Clinical Trials.gov дерекқорларында іздеу жүргізілді. Іздеу үшін «ұсақ жасушалы емес өкпе обыры», «отоуыттылық әсер», «гефитиниб», «эрлотиниб», «афатиниб», «дакомитиниб» және «осимертиниб» кілт сөздері қолданылды.*

Нәтижелері: *EGFR ішкі құлақтың сенсорлық және сенсорлық емес құрылымдарын дамытуда, сақтауда және қалпына келтіруде маңызды рөл атқарады. Неонатальды модельдерде EGFR кохлеарлы жасушаларда, соның ішінде Корти орган, онда ол регенерация мен қалпына келтіру процестерін жеңілдетеді. Алайда, жетілген жүйелерде EGFR экспрессиясы төмен-дейді, ең алдымен есту жасушаларының регенеративті қабілетін шектейтін спиральды ганглияда орналасады. EGFR дабылын тежеу арқылы жасуша пролиферациясы мен қалпына келтіру механизмдері бұзылады, бұл кохлеарлық шаш жасушалары мен тірек жасушаларына зақым келтіреді.*

Қорытынды: *TKI-индукцияланған отоуыттылықтың нақты таралуы мен негізгі молекулалық механизмдері аз зерттелген. Дозаға тәуелді әсерлерді, генетикалық бейімділікті және ықтимал қорғаныс стратегияларын анықтау үшін қосымша зерттеулер қажет. Бұл жағымсыз әсерді білу EGFR-TKI терапиясы кезінде есту денсаулығын бақылау және оның ұзақ емделетін науқастарға әсерін жеңілдететін араласуларды зерттеу үшін қажет.*

Түйінді сөздер: *өкпенің ұсақ жасушалы емес қатерлі ісігі, эпидермиялық өсу факторының рецепторы, тирозинкиназа ингибиторлары, отоуыттылық.*

АННОТАЦИЯ

ПОТЕНЦИАЛЬНАЯ ОТОТОКСИЧНОСТЬ РАЗНЫХ ПОКОЛЕНИЙ ИНГИБИТОРОВ ТИРОЗИНКИНАЗЫ *EGFR*: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак легкого – часто диагностируемое злокачественное новообразование. Немелкоклеточный рак легкого (НМРЛ) составляет примерно 85% случаев рака легкого. Ключевым фактором развития НМРЛ является мутация гена рецептора эпидермального фактора роста (EGFR), который играет ключевую роль в возникновении и прогрессировании опухоли. Появление ингибиторов тирозинкиназы (ИТК), нацеленных на EGFR, ознаменовало значительный прогресс,*

предложив более рациональный и эффективный терапевтический подход. Ингибиторы тирозинкиназы не лишены побочных эффектов. Появляются данные, указывающие на потенциальную связь между терапией ИТК и ототоксичностью. Учитывая хронический характер лечения пациентов с запущенной стадией заболевания, даже незначительная токсичность может существенно повлиять на качество жизни. Важно информировать пациентов о потенциальном риске ухудшения слуха, осуществлять регулярный мониторинг ранних признаков ототоксичности для оптимизации долгосрочных результатов лечения пациентов.

***Цель исследования** – изучение существующих данных об ингибиторах тирозинкиназы, их потенциальной ототоксичности, включая основные механизмы патогенеза.*

***Методы:** Поиск проводился по базам данных PubMed, Scopus, Embase, Cochrane Library, Web of Science, Google Scholar и Clinical Trials.gov для выявления научных публикаций об ототоксичности, вызванной приёмом ингибиторов тирозинкиназы при НМРЛ. Для поиска использовались ключевые слова «немелкоклеточный рак лёгкого», «ототоксичность», «гефитиниб», «эрлотиниб», «афатиниб», «дакомитиниб» и «осимертиниб».*

***Результаты:** EGFR играет важную роль в развитии, поддержании и восстановлении сенсорных и несенсорных структур внутреннего уха. В неонатальных моделях EGFR экспрессируется в кохлеарных клетках, включая кортиев орган, где он облегчает процессы регенерации и восстановления. Однако в зрелых системах экспрессия EGFR снижается, в первую очередь локализуясь в спиральном ганглии, ограничивая регенеративную способность слуховых клеток. Ингибируя сигнализацию EGFR, нарушается клеточная пролиферация и механизмы восстановления, что приводит к повреждению волосковых клеток улитки и поддерживающих клеток.*

***Заключение:** Точная распространенность и основные молекулярные механизмы ототоксичности, вызванной ИТК, остаются плохо изученными. Необходимы дальнейшие исследования для выяснения дозозависимых эффектов, генетической предрасположенности и потенциальных защитных стратегий. Знание этого неблагоприятного эффекта необходимо для мониторинга слухового здоровья во время терапии EGFR-TKI и для изучения вмешательств, которые смягчают его влияние на пациентов, проходящих длительное лечение.*

***Ключевые слова:** немелкоклеточный рак легкого (НМРЛ), рецептор эпидермального фактора роста, ингибиторы тирозинкиназы (ИТК), ототоксичность.*

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