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Adverse Drug Reactions Associated with Oral EGFR-Targeted Therapy in Non-Small Cell Lung Cancer: A Comprehensive Analysis

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Abstract. Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKIs) have revolutionized the treatment of Non-Small Cell Lung Cancer (NSCLC). However, their utility is often limited by distinct Adverse Drug Reactions (ADRs). This review analyzes the safety profiles of three representative oral EGFR-TKIs: Gefitinib (1st-generation), Afatinib (2nd-generation), and Osimertinib (3rd-generation). We examine the relationship between their pharmacokinetic mechanisms and specific organ toxicities.First-generation agents (Gefitinib) are associated with cutaneous and hepatic toxicities due to inhibition of wild-type EGFR and CYP450-mediated metabolism. Second-generation agents (Afatinib), as irreversible Pan-HER inhibitors, exhibit increased mucocutaneous and gastrointestinal toxicity. Third-generation agents (Osimertinib) demonstrate improved selectivity for EGFR-mutant forms, reducing wild-type-mediated toxicity, though they introduce unique risks, such as QTc prolongation. The evolution of EGFR-TKIs reflects a shift toward higher selectivity and improved safety profiles. Understanding these generational differences is critical for optimizing patient adherence and developing personalized management strategies.

Keywords: NSCLC, EGFR-TKI, Pharmacovigilance, Hepatotoxicity, Cardiotoxicity

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide. According to the latest global cancer statistics, there were approximately 2.5 million newly diagnosed cases and 1.8 million deaths attributed to the disease in the most recent reporting year [1]. Histologically, lung cancer is classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all cases [2]. Despite advances in early detection, a significant proportion of patients are diagnosed at an advanced stage, where the 5-year survival rate remains critically low [2].

The discovery of activating mutations in the epidermal growth factor receptor (EGFR) gene has revolutionized the treatment landscape for advanced NSCLC. The introduction of oral EGFR tyrosine kinase inhibitors (TKIs) has shifted the standard of care from cytotoxic chemotherapy to

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precision medicine, significantly improving progression-free survival [3]. Currently, clinical practice utilizes three distinct generations of EGFR-TKIs: first-generation reversible inhibitors (e.g., gefitinib), second-generation irreversible ErbB blockers (e.g., afatinib), and third-generation mutant-selective inhibitors (e.g., osimertinib) [3].

However, the clinical utility of these agents is frequently compromised by their adverse drug reaction (ADR) profiles. First-generation agents like gefitinib are associated with significant hepatotoxicity due to their metabolic pathways and inhibition of wild-type EGFR [4]. Second-generation agents, such as afatinib, exhibit a broader inhibitory profile but are often dose-limited by severe mucocutaneous toxicity, particularly diarrhea [5]. While the third-generation agent osimertinib demonstrates improved selectivity for mutant EGFR, recent pharmacovigilance data indicate a distinct risk of cardiotoxicity, including QTc interval prolongation and heart failure, which was less prevalent in earlier generations [6].

As the use of these targeted therapies expands into adjuvant and first-line settings, understanding the evolution of their safety profiles is critical. This review provides a comparative analysis of the adverse reactions associated with gefitinib, afatinib, and osimertinib. By synthesizing data from recent meta-analyses and clinical trials, we aim to highlight the generational shift in toxicity mechanisms and provide evidence-based guidance for clinical monitoring and management.

2. Inhibitory mechanism of drugs on NSCLC

2.1. First-generation EGFR-TKIs: gefitinib

Gefitinib functions as a reversible, small-molecule tyrosine kinase inhibitor that competitively binds to the adenosine triphosphate (ATP)-binding pocket of the EGFR kinase domain. By preventing ATP binding, the drug inhibits the receptor's autophosphorylation, thereby blocking downstream signaling cascades, such as the RAS/RAF/MEK and PI3K/AKT pathways, which are essential for tumor cell proliferation. However, because gefitinib also inhibits wild-type EGFR in healthy tissues, it frequently induces cutaneous toxicities. The landmark IPASS study established that while gefitinib significantly improved progression-free survival compared to chemotherapy in select populations, it was associated with a 66.2% incidence of rash or acne [7].

The mechanism underlying this dermatologic toxicity is directly linked to the physiological role of EGFR in the skin. EGFR is highly expressed in basal keratinocytes, where it regulates cell survival and differentiation. The inhibition of these receptors by gefitinib leads to premature keratinocyte apoptosis and the subsequent release of inflammatory chemokines, resulting in the characteristic papulopustular rash often observed in the first weeks of therapy [8].

Unlike other class members, gefitinib also poses a specific risk of hepatotoxicity. The drug is extensively metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4 and CYP2D6. Research indicates that genetic polymorphisms in CYP2D6 can lead to inter-individual variability in drug exposure, contributing to hepatocellular injury. Clinical data suggest that elevated alanine aminotransferase (ALT) levels are a frequent adverse event, with Grade 3 or higher hepatotoxicity occurring in a subset of patients, necessitating routine liver function monitoring during treatment [9].

2.2. Second-generation EGFR-TKIs: afatinib

Afatinib is the second-generation TKI and acts as an irreversible inhibitor of the ErbB family. Unlike the reversible binding of gefitinib, afatinib contains a reactive acrylamide group that forms

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permanent covalent bonds with specific cysteine residues within the kinase domains of EGFR (Cys773), HER2, and HER4 [10]. This irreversible binding results in a more sustained and potent inhibition of the receptor family, effectively blocking signaling from all homo- and heterodimers formed by ErbB family members.

While this broad-spectrum "Pan-HER" inhibition enhances therapeutic efficacy, it also broadens the toxicity profile, particularly with respect to mucocutaneous and gastrointestinal adverse effects. The pivotal LUX-Lung 3 trial demonstrated that diarrhea was the most common adverse event, affecting 95% of patients treated with afatinib, with 14.4% experiencing Grade 3 severity [11]. The mechanism of this toxicity is attributed to the drug's potent inhibition of wild-type EGFR in the intestinal epithelium, which disrupts the regulation of chloride secretion and sodium absorption, leading to secretory diarrhea that can be dose-limiting.

2.3. Third-generation EGFR-TKIs: osimertinib

Osimertinib is used to treat non-small cell lung cancer (NSCLC) harboring specific mutations (e.g., the EGFR T790M mutation). It works by irreversibly binding to the EGFR mutant protein to block tumor cell growth signals, exhibiting significant inhibitory effects, particularly against EGFR-sensitizing mutations and the EGFR T790M resistance mutation. In vivo, it is primarily metabolized by the cytochrome enzymes CYP3A4 and CYP3A5. Common adverse reactions to osimertinib include diarrhea, dry skin, rash, and nail toxicity. Severe adverse reactions, such as QTc interval prolongation on electrocardiograms, interstitial pneumonia, and pulmonary embolism, occur occasionally. Gastrointestinal adverse reactions also occur, though severe cases are rarely reported [11]. This article focuses on the cardiotoxicity manifested during treatment with osimertinib.

The cardiotoxic effects of osimertinib include QT interval prolongation, atrial fibrillation, decreased left ventricular ejection fraction (LVEF), and even heart failure; however, the mechanisms are not yet fully understood. As one of its severe adverse reactions, QT interval prolongation may induce ventricular tachycardia, often necessitating drug discontinuation and significantly delaying the treatment course. Animal studies have confirmed that QT interval prolongation may be associated with osimertinib's inhibition of the phosphatidylinositol-3-kinase (PI3K) pathway. In canine cardiomyocytes, osimertinib inhibits PI3K signaling, leading to alterations in multiple ion channel currents that ultimately prolong the QT interval. Therefore, during the clinical use of osimertinib, medical personnel must be vigilant regarding the risk of QT interval prolongation and strengthen monitoring and management for high-risk patients [12] to facilitate timely adjustments to the treatment regimen.

3. Manifestations and principles of drug-induced adrs

The most common toxicities of gefitinib are gastrointestinal toxicity and skin toxicity. However, most of the symptoms of the above two adverse reactions are mild and within the tolerance range of patients, and usually do not require drug discontinuation. At the same time, more serious adverse reactions include bone marrow suppression, interstitial lung disease, and liver toxicity [12]. This article focuses on representative skin and liver toxicity for discussion.

3.1. Skin toxicity

Studies have shown that the incidence of skin toxicity caused by gefitinib is 30% to 87%, which seriously affects the quality of life of patients. Its mechanism of action can be summarized as

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follows: EGFR-TKIs promote keratinocyte apoptosis, leading to excessive differentiation and migration, altering cell state, and causing abnormal cell migration and adhesion in the epidermis, and damaging tight junctions [13]. At the same time, the inflammatory response of cells is also a crucial factor in EGFR-TKIs-induced skin toxicity, as there is a mutual regulatory effect between the epidermal barrier function and inflammation activation. Therefore, when the EGFR signaling in the epidermis is disrupted, a series of inflammatory cascades will occur, leading to disruption of the skin barrier and further aggravating inflammation. Inhibition of the EGFR signaling pathway leads to increased abnormal skin fat metabolism and impaired sebum excretion, thereby triggering inflammatory reactions and rashes [13]. Common skin toxicity reactions include itching, dry skin, mild rashes, and inflammation of the nail folds and nail tissues. These conditions can usually be prevented and relieved by using sun protection, keeping the skin clean and moisturized, and wearing loose and breathable clothing. However, severe adverse reactions such as severe exfoliative rashes and erythema multiforme infection with ulcers have also been reported [14]. Therefore, it is clear that gefitinib-induced skin adverse reactions should not be underestimated. If patients experience severe skin toxicity reactions, they should seek medical attention in time to avoid delaying the condition.

Moreover, the adverse reactions caused by afatinib also involve the skin and its appendages. The mechanism by which afatinib triggers ADRs in the skin and its appendages is similar to that of gefitinib. Both drugs' inhibition of EGFR disrupts normal epidermal differentiation and re-epithelialization, leading to extensive skin damage. Such adverse reactions often occur in areas with abundant sebaceous glands. In severe cases, the lower limbs and, in some cases, the entire body of the patient may be affected. The main manifestations include rashes, acneiform rashes, paronychia, and eczema. The adverse reaction grades are mostly below grade 3. Severe cases may present as SJS, DRESS, or other conditions [14].

3.2. Hepatotoxicity

The mechanism of liver toxicity caused by gefitinib is related to its pharmacokinetic properties. The metabolism of gefitinib primarily occurs through cytochrome P450 3A4 (CYP3A4) and CYP2D6 in the liver [12]. Its PK-pADIs may lead to an increase in adverse reactions and a decrease in therapeutic effects, thereby affecting the safety of gefitinib. The polymorphism and activity of CYP3A4 and CYP2D6 can significantly affect the metabolism of gefitinib. The former reduces the drug's metabolic rate, while the latter increases the risk of gefitinib-related liver toxicity by inhibiting the function of transport proteins. Specific CYP2D6 genotypes in NSCLC are highly correlated with severe liver toxicity cases, indicating a strong association between individual metabolic differences and gefitinib-induced liver toxicity [15]. Personalized treatment plans should be developed for patients when necessary. In clinical practice, the incidence of grade 3 or higher liver toxicity caused by gefitinib is as high as 26%, and such patients often face delays or even termination of treatment [12]. The liver toxicity of gefitinib seriously endangers the health of patients with NSCLC and largely delays the treatment process.

3.3. Respiratory and gastrointestinal toxicity

Respiratory adverse reactions caused by afatinib are mainly interstitial lung disease, and the mechanism is still unclear. It may be related to direct damage caused by drug toxicity or immune-mediated inflammatory reactions. Interstitial lung disease can seriously affect the patient's respiratory function and thus threaten the patient's life. For patients taking afatinib, if they

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experience symptoms similar to pneumonia, such as shortness of breath and rapid breathing, the possibility of ILD caused by the drug should be carefully considered. At the same time, there are cases indicating that patients with EGFR mutations developed severe interstitial pneumonia complications during afatinib treatment, suggesting that genetic testing may be an essential means to predict and prevent adverse reactions caused by targeted drugs [15].

The inhibition of EGFR expression on the surface of the digestive tract mucosa by afatinib may be a significant cause of its adverse reactions in the digestive tract. The most common form is diarrhea. Dehydration caused by diarrhea may increase afatinib's blood concentration, thereby increasing the burden on patients' livers and kidneys.

3.4. Cardiotoxicity

Diarrhea, dry skin, rash, and nail toxicity are common adverse reactions of osimertinib. Occasionally, severe adverse reactions such as QTc interval prolongation, interstitial pneumonia, and pulmonary embolism may occur. Gastrointestinal adverse reactions also occur, but severe cases are rarely reported [16]. This article focuses on cardiac toxicity associated with osimertinib during treatment.

The cardiac toxicity of osimertinib mainly includes QT interval prolongation, atrial fibrillation, decreased left ventricular ejection fraction, and even heart failure. The mechanism is not yet obvious. As one of its severe adverse reactions, QT interval prolongation may induce ventricular tachycardia and often requires drug withdrawal, seriously delaying the treatment process. Animal experiments have confirmed that QT interval prolongation may be associated with osimertinib inhibition of the phosphatidylinositol-3-kinase (PI3K) pathway. Osimertinib inhibits PI3K signaling in canine cardiomyocytes, leading to changes in multiple ion channel currents and ultimately resulting in QT interval prolongation. Therefore, when using osimertinib in clinical practice, medical staff must be vigilant about the risk of QT interval prolongation and strengthen monitoring and management for high-risk patients [12] to promptly adjust the treatment plan.

4. Research significance and future prospects

The comparative analysis of first-, second-, and third-generation EGFR-TKIs reveals a distinct evolutionary trajectory toward "precision safety," characterized by a shift from non-specific adverse events to mechanism-based, organ-specific toxicities. The defining limitation of early-generation agents, particularly gefitinib and afatinib, lies in their "on-target, off-tumor" effects. Because these drugs exert significant inhibitory pressure on wild-type EGFR, which is abundantly expressed in the basal layer of the epidermis and the gastrointestinal mucosa, they are intrinsically linked to high rates of cutaneous and gastrointestinal adverse events. As evidenced by the IPASS and LUX-Lung trials, these mucocutaneous toxicities are not merely cosmetic; they significantly impair patient quality of life and frequently necessitate dose reductions that may compromise therapeutic efficacy.

The development of osimertinib marks a pivotal divergence in this safety profile. By structurally targeting the ATP-binding pocket with high selectivity for EGFR-mutant forms while sparing the wild-type receptor, osimertinib effectively decouples therapeutic efficacy from epithelial toxicity. This "decoupling" effect was clearly demonstrated in the comparative safety data from the FLAURA trial, where the incidence of Grade 3 or higher rash and diarrhea was markedly lower in the osimertinib arm than in the gefitinib/erlotinib arm. This reduction in symptomatic burden represents a substantial advancement in long-term tolerability, enabling patients to remain on therapy for more extended periods with fewer interruptions.

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However, the assertion that the field is moving solely toward a "safer" direction requires nuance. While the third generation minimizes the classic EGFR toxicities (rash and diarrhea), it introduces a distinct cardiovascular risk profile that was largely absent in earlier generations. The emergence of cardiotoxicity, specifically QTc prolongation and cardiomyopathy, suggests that the safety profile has not just improved but shifted. This necessitates a change in pharmacovigilance strategies. Whereas the management of gefitinib and afatinib focuses heavily on proactive skin care and aggressive anti-diarrheal protocols, the management of osimertinib requires a shift toward cardiac monitoring, including baseline and periodic electrocardiograms (ECGs) and assessment of left ventricular function, particularly in patients with pre-existing cardiac comorbidities.

5. Conclusion

The three representative oral EGFR-targeted drugs discussed in this article (gefitinib, afatinib, and osimertinib) all induce varying degrees of adverse reactions, primarily cutaneous (e.g., rash, dry skin), gastrointestinal (e.g., diarrhea), and pulmonary (e.g., ILD/pneumonitis), sharing similar underlying mechanisms. However, distinct generational differences are evident. Compared with the first-generation drug gefitinib, reports of severe skin and gastrointestinal toxicities, as well as hepatotoxicity, have significantly decreased with afatinib and osimertinib. Nevertheless, this evolution does not imply a simple elimination of all risks. While the third-generation drug osimertinib demonstrates improved tolerability regarding traditional side effects, it introduces new safety concerns, particularly cardiotoxicity (e.g., QT prolongation and heart failure), which were less prominent in earlier generations. Therefore, the development of EGFR-targeted drugs is generally moving towards a safer direction in terms of overall tolerability, but it is characterized by a shift in toxicity profiles rather than a uniform reduction in all adverse events. Understanding these universalities and specific generational differences is vital for optimizing clinical management and guiding the development of future targeted therapies.

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