Curr Cancer Rep, 2025, 6(1): 248-253
DOI: 10.25082/CCR.2024.01.006

REVIEW

Skin toxicities related to targeted therapy and immunotherapy for non-small cell lung cancer

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Received: November 5, 2024;
Revised: January 18, 2025;
Accepted: March 2, 2025;
Published: March 20, 2025.

Citation: Yan J, Zhang M. Skin toxicities related to targeted therapy and immunotherapy for non-small cell lung cancer. *Curr Cancer Rep*, 2025, **6**(1): 248-253. https://doi.org/10.25082/CCR.2024.01.006

Abstract: Non-small cell lung cancer (NSCLC) is the most common cancer, causing death and disability. Targeted therapy and immunotherapy have had an increasing role in the management of patients with advanced NSCLC. These treatments can produce an excellent curative effect, but the side effects should not be ignored. Skin toxicities such as papulopustular eruption, severe desquamation, and paronychia have a high incidence, seriously affecting patients' quality of life and even interrupting treatment. Early recognition and adequate management are critical to prevent exacerbation of the lesions. This review describes the common skin toxicities related to targeted therapy and immunotherapy for NSCLC, summarizes the updated research progress of the mechanism, and proposes appropriate treatment and counseling for optimized management.

Keywords: non-small cell lung cancer, immunotherapy, targeted therapy, skin toxicities

1 Introduction

Lung cancer is the malignant tumor with the highest incidence and mortality worldwide, among which non-small cell lung cancer (NSCLC) accounts for 80% to 85% of total lung cancer. The vast majority of patients have local spread or distant metastasis when they go to the hospital and lose the opportunity for surgery. At present, the treatment of advanced NSCLC mainly includes chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Currently, targeted therapies for NSCLC include inhibitors targeting EGFR, ALK, ROS1, RET, KRAS, HER2, BRAF, and other driver genes, such as gefitinib and trastuzumab. Immunotherapy includes tumor vaccines and immune checkpoint inhibitors, such as the CTLA-4 inhibitor ipilimumab and the PD-1 inhibitor Opdivo. While achieving good clinical efficacy, these targeted immunotherapies may bring many adverse effects, such as dizziness, vomiting, hypertension, chest pain, weight loss, and other products. It has been reported that 50%-80% of patients taking EGFR inhibitors and MEK inhibitors have skin toxicity, which seriously affects the quality of life and even leads to treatment interruptions [1]. These cutaneous toxic reactions usually develop within a few weeks of initial treatment, are mostly dose-dependent, and would resolve after drug reduction or withdrawal. Common cutaneous toxic reactions include papulopustular eruption on the scalp, severe desquamation, paronychia, alopecia, trichomegaly, acneiform eruption, xerosis and desquamation, painful fissure, alopecia and other reactions [2].

In 2021, Gisondi et al. [3] assess the incidence, impact on treatment and management of EGFR inhibitor-related cutaneous reactions in patients with NSCLC, and found that 81.6% of patients developed cutaneous reactions and afatinib was associated with a higher rate of nail changes and mucositis compared to other agents. Peng et al. [4] examined the types and frequencies of dermatologic toxicities associated with anti-epidermal growth factor receptor (EGFR) therapies in NSCLC and metastatic colorectal carcinoma and proposed the management and treatment options. To sum up, there have been some studies on the skin toxicities associated with anti- epidermal growth factor receptor (EGFR) therapies in NSCLC, and summarize the incidence, severity, and management of these skin toxicities [5]. However, the mechanism is still unclear, and whether the severity is correlated with therapeutic efficacy, whether treatment should be discontinued in the presence of skin toxicities, and whether the treatment procedure should be continued after the skin toxicities are resolved to remain controversial. Further summaries and studies are needed to solve the problem.

2 Immunotherapy of non-small cell lung cancer

Compared with traditional cytotoxic chemotherapy, immunotherapy is associated with a higher response rate, improved overall survival (OS), and increased tolerance. The appearance of blocking immune checkpoints has completely changed the management of advanced non-small cell lung cancer (NSCLC). Some researchers found that resecting NSCLC specimens after using immunosuppressants showed an encouraging pathological response rate.

ICI can activate the antitumor immune response mediated by previously inhibited T cells by blocking the internal downstream immune regulatory factors while maintaining the dynamic interaction between differentiation cluster (CD) 8+T cells, antigen-presenting cells, and tumor cells [6]. Currently, the primary immune antibodies used in the clinical treatment of lung cancer are pemomab, Navulizumab, tanezumab, Iprimma, and Duvalumab. Pimmumab and Navuliu McAb mainly block PD-1, tanezumab, and Duvalumab block PD-L1, and Iprimma McAb is an anti-CTLA-4 antibody. It was found that anti-PD-1 mainly induced the expansion of specific tumor infiltration failures like CD8 T cell subsets. On the contrary, anti-CTLA-4 increased ICOS+Th1-like CD4 effector cell populations. However, different cellular mechanisms drove the immune responses induced by both, they both showed significant immunosuppressive effects [7], And the two may have a synergistic anti-tumor effect. A researcher conducted a clinical trial in patients with advanced NSCLC. The patients were divided into two groups according to the level of PD-L1 expression (1%), and each group was randomly divided into three groups for Navurizumab+Iprimumab, receiving Navurizumab alone and chemotherapy alone. Finally, it was found that there was no relationship with PD-L1 expression level. In NSCLC patients, the overall survival period of first-line treatment with Navulizumab plus Iprimma was longer than that of chemotherapy, which further indicated the long-term effect of immunotherapy [8]. Nivolumab is an all-human IgG4 antibody against PD-1. The most common adverse reactions of patients receiving Nivolumab as a single drug are fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, weakness, cough, dyspnea, constipation, loss of appetite, back pain, joint pain, upper respiratory tract infection, fever, headache, abdominal pain, and vomiting. Among them, the percentage of patients with rash reached 10% [9]. Pembrolizumab is a humanized IgG4 antibody targeting PD-1. The most common adverse reactions of patients treated with Pembrolizumab as a single drug are fatigue, musculoskeletal pain, loss of appetite, pruritus, diarrhea, nausea, rash, fever, cough, dyspnea, constipation, and abdominal pain [10]. Atezolizumab is a humanized IgG1 antibody targeting PD-L1. The most common adverse reactions of patients treated with Atezolizumab as a single drug are fatigue, nausea, cough, dyspnea, and loss of appetite. Ipilimumab is an all-human IgG1 kappa antibody against CTLA-4. The most common adverse reactions of Iprimma single drug are fatigue, diarrhea, pruritus, rash, colitis, nausea, vomiting, headache, weight loss, fever, loss of appetite, and insomnia. Durvalumab is an all-human IgG1 kappa antibody against PD-L1. The most common adverse reactions of Durvalumab as a single drug are fatigue, constipation, rash, nausea, dyspnea, swelling of arms and legs, and loss of appetite. It can be seen that five immunotherapeutic drugs for lung cancer can lead to adverse skin reactions to varying degrees, the most common of which are skin rashes and itching.

3 Targeted therapy of non-small cell lung cancer

The understanding of genetic alterations that drive NSCLC is evolving, and a new landscape of treatment in lung cancer emerged with the advent of directed therapy toward certain driver genetic alterations. It is reported that molecular alterations such as EGFR mutations, ALK rearrangements, ROS1 rearrangements, and BRAF V600E mutations are present in approximately 30% of patients with NSCLC [11], and targeted therapy for these alterations improves progression-free survival compared with cytotoxic chemotherapy. From this point of view, targeted therapies are considered anticancer drugs designed to inhibit the protein products of activated oncogenes or their resultant pathways. KRAS is one of the most frequently altered genes in NSCLC and co-mutations occurring with KRAS dictate the immune infiltrate and define distinct subgroups of KRAS-mutant lung cancer. Koyama et al. [12] found that STK11/LKB1 deficiency promotes neutrophil recruitment and proinflammatory cytokine production to suppress T-cell activity in the lung tumor microenvironment. For EGFR mutation- positive lung cancer, targeted therapy demonstrates a significant benefit when used in the early postoperative setting. Wu et al. [13] conducted a double-blind, phase 3 trial including 682 completely resected EGFR mutation-positive NSCLC, and evaluated the overall survival and safety of Osimertinib. Results show that 98% of the patients in the osimertinib group and 85% of those in the placebo group were alive and did not have central nervous system disease at 24 months follow-up. Zhong

et al. [14] found that the progression-free survival of patients with stage IIIA-N2 NSCLC is longer in the erlotinib group than that in the gemcitabine plus cisplatin group.

4 The occurrence of skin toxicities during targeted therapy and immunotherapy

Although targeted therapy and immunotherapy could improve the progression-free survival of advanced NMSC, adverse events can never be neglected. The checkpoint antibodies, including PD-1, PD-L1, and CTLA-4 antibodies, can lead to autoimmune or inflammatory toxicities in almost any organ system, such as the gastrointestinal system, endocrine glands, skin, liver, lung, and other organs. Mucocutaneous toxicities were the most common side effect affecting approximately 45–100% of patients [15]. Gisondi et al. [3] The incidence of EGFR inhibitor-related cutaneous reactions were assessed in patients with NSCLC, and 71 in 87 patients developed cutaneous reactions. The most common cutaneous reactions included acneiform eruptions, dry skin, asteatotic eczema, nail changes, mucositis, pruritus, and hair changes. Roé et al. [16] reported cutaneous side effects during cetuximab or erlotinib treatments and found that follicular eruption, painful fissures in palms and soles, and, paronychia, hair growth changes are common skin toxicities. An open-label phase II trial of neoadjuvant erlotinib for patients with early-stage NSCLC included 60 patients, 37 patients (62%) presented skin rash, 13 patients (22%) presented dry skin and 7 patients (12%) complained of pruritus [17]. Most toxicities are mild and resolved within 7 days, but one patient showed an acneiform skin rash up to 3 weeks after the end of treatment.

A previous study found that the occurrence of cutaneous side effects varies on the gender and age of patients. Chandra et al. [18] found that female patients had more xerosis cutis and paronychia, while male patients experienced more acneiform eruption. Xerosis cutis and acneiform eruption were the two most common cutaneous findings in every age group, while paronychia was detected mostly in the 40–44 and 60–64 age groups.

5 Possible mechanism of skin toxicities

Cetuximab has a significant therapeutic effect on metastatic diseases, but in about 80% of patients, cetuximab will cause disfiguring skin toxicity, mainly in the face and neck. In the beginning, the skin lesions were diffuse facial erythema, desquamation, and dry skin in the neck, accompanied by diffuse and itchy folliculitis similar to can. Then they developed into pustules, forming a firmly adhered pale yellow scab.

Research shows that papules and pustules are often accompanied by telangiectasia, similar to rosacea. These acne-like rashes are usually associated with microbial infections. In persistent lesions, bacterial colonization of Staphylococcus aureus and detection of herpes simplex type I is not uncommon. K.J. Busam and et al. found that the disruption in the growth and differentiation of the hair follicle by EGFR inhibitors may contribute to the follicular localization of the acneiform eruption, neutrophilic folliculitis, and perifolliculitis [19]. This disruption may cause a mechanical rupture of the hair follicle, leading to hyperkeratosis, follicular plugging, and eventual obstruction of the follicular ostium. Paronychia occurs less frequently than acneiform eruptions, and the histopathologic evaluation of paronychia shows marked inflammation in the dermis consisting mainly of plasma cells, lymphocytes, and neutrophils. In 15% of cases, skin manifestations may be very severe, leading to skin necrosis, nail changes (paronychia), inflammation with red eyes, tears, sensitivity to light, and blurred vision [20]. After using immune checkpoint inhibitors, eczema and bacterial superinfection may occur in areas with poor infection resistance [21].

It has also been reported that the toxic skin symptoms related to EGFR-TK inhibitors may be associated with the release of IL-31 and IL-33. The researchers found that EGFR-TK inhibitors may cause keratinocytes damage, IL-33 release, and subsequent interaction with its receptor on mast cells, thus inducing the secretion of a variety of factors that can cause skin performance, including IL-31, known as itch-inducing cytokine [22].

6 The management of skin toxicities

Because of the high incidence and the frequent discomfort of skin toxicities during anti-tumor therapy, effective management is necessary. It is recommended to solve this problem according to its severity. For mild cases, the lesions sometimes resolve spontaneously despite continued

treatment, and so treatment is unnecessary. To be specific, acneiform eruptions are one of the most common skin toxicities, and occur in the face and neck, affecting the patient's beauty. In mild and moderate cases, conventional topical antiacne medications, such as benzoyl peroxide, metronidazole, erythromycin, and clindamycin could be used to relieve these side effects [23]. If the lesions are moderate to severe with pruritus, oral tetracycline and an oral antihistamine can be taken in addition to topical medications [24]. Oral isotretinoin has also been effective, but its use should be approached with caution for it may aggravate paronychia and xerosis [25, 26]. As for paronychia, the management involves both preventive measures and treatment of the inflammation and possible infection. Firstly, patients should avoid friction and pressure on the nail fold. And then some medications could be used to relieve symptoms. Topical steroids, such as 0.1% triamcinolone can alleviate the pain and inflammation, and topical antimicrobial agents such as mupirocin or nystatin ointment can resolve both anti-inflammatory properties and antimicrobial properties [27]. For paronychia with periungual granulation tissue, topical silver nitrate or the combination of topical dressings, disinfection, and topical steroids can be helpful [28]. Xerosis often affects more widespread areas causing painful fissures on the tips of fingers and toes, of the nail folds, and over the interphalangeal joints, and even discomfort during urination. Topical emollients are the main treatment method, and short-term, low-dose corticosteroids can be used for eczema. Topical or systemic antibiotics should be used when infected [29]. And in some cases, telangiectasias occur together with acneiform eruptions and usually first appear on the face, chest, back, and limbs, The telangiectasias will gradually fade with time, and electrocoagulation or pulsed dye laser therapy can be applied to accelerate disappearance [26]. Hyperpigmentation appears to be mostly post-inflammatory, so adequate prevention and treatment of acneiform eruption are important. Protect from sun exposure can help to minimize the risk of hyperpigmentation.

Additionally, since most skin toxicities are dose-dependent, modifying the dosage or dosing schedule of the targeted therapy and immunotherapy can help manage the lesions and discomforts.

7 Conclusion

The targeted therapy and immunotherapy for NSCLC are associated with a unique group of class-specific skin toxicities, which include acneiform eruption, paronychia, xerosis, telangiectasia, and hyperpigmentation. The underlying mechanisms are poorly understood but are most likely linked to nonspecific targets in the skin and the release of inflammatory cytokines. The discomfort caused by these skin toxicities can reduce compliance with anti-tumor therapy, so dermatologists and oncologists need to be aware of and be able to effectively treat these side effects. Topical antiacne medications and be used for acneiform eruptions, and emollient cream is recommended for the xerosis. In some cases, the adverse reactions are serious and topical drugs do not work, it is suggested to suspend the anti-tumor therapy. When and how to continue anti-tumor therapy should be evaluated by both dermatologists and oncologists. Future clinical research is required to meet the need for more accurate classification and more evidence-based treatment of skin toxicities.

Conflicts of interest

The authors declare no conflict of interest.

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(Edited by Snowy Wang)