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Editorial

Skin Toxicity of Target Therapies, Immunotherapy and New Cancer Vaccines

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Abstract

The new treatments for tumor diseases have been for about 20 years, a huge advance in medicine in general and oncology in particular. With target therapies, tyrosine kinase inhibitors, monoclonal antibodies, antitumor vaccines and new molecules under investigation, unthinkable responses are being achieved, for example, in melanoma, lung cancer, breast cancer and other tumors, what we do not fully know yet is the toxicity of these treatments.

The skin, the largest organ of the human being, is no stranger to this toxicity.

In this article we review this toxicity, its pathophysiology and its treatment.

Keywords: Lung Cancer; Breast Cancer; Oncology

Introduction

Targeted therapies, immunotherapies, and new cancer vaccines have revolutionized cancer treatment in recent years. While they offer significant benefits, they can also have certain side effects, including skin toxicity.

Targeted therapies work by targeting specific molecules or proteins involved in cancer growth. Some of these therapies, such as EGFR inhibitors or BRAF inhibitors, have been associated with skin toxicities. Common skin-related side effects may include rash, dryness, itching, or changes in pigmentation. These reactions can vary in severity and may require intervention or dose adjustments.

Immunotherapies, such as checkpoint inhibitors like PD-1 or CTLA-4 inhibitors, harness the body's immune system to fight cancer. While these treatments can be highly effective, they can also lead to immune-related adverse events, including dermatological toxicities. Skin reactions like rash, pruritus (itching), or blistering can occur as a result of the immune system's response.

New cancer vaccines, such as therapeutic vaccines or personalized neoantigen vaccines, are emerging as promising approaches. Skin reactions at the injection site are a common occurrence with vaccines, and cancer vaccines are no exception. Localized skin redness, swelling, or discomfort are typically temporary and resolve without complications.

It's important to note that the specific skin toxicities and their severity can vary depending on the individual, the type of therapy, and the specific cancer being treated. If you or someone you know is experiencing skin-related side effects from any cancer treatment, it's essential to communicate with the healthcare team to manage these symptoms effectively.

Why do these toxic effects occur, what is the pathophysiology?

The skin toxic effects observed with targeted therapies, immunotherapies, and cancer vaccines occur due to various mechanisms related to the drugs' mode of action and their impact on the body's systems.

With targeted therapies, such as EGFR inhibitors or BRAF inhibitors, the drugs interfere with specific molecules or pathways involved in cancer cell growth. However, these pathways are also important for normal skin function. By inhibiting or altering these pathways, targeted therapies can disrupt the normal balance and functioning of skin cells, leading to skin toxicities. The specific mechanisms behind these toxic effects may include inflammation, altered cell signaling, or interference with cell proliferation and differentiation.

Figure 1

Immunotherapies, particularly checkpoint inhibitors like PD-1 or CTLA-4 inhibitors, work by removing the brakes on the immune system, allowing it to recognize and attack cancer cells. However, this enhanced immune response can also affect normal tissues, including the skin. The immune system may recognize certain skin cells as foreign or abnormal, leading to inflammation and immune-mediated toxicities. The exact mechanisms behind immune-related dermatological toxicities are still being investigated but may involve immune cell infiltration, cytokine release, or autoimmune reactions targeting skin antigens.

Cancer vaccines, including therapeutic or personalized neoantigen vaccines, aim to stimulate the immune system to recognize and target cancer cells. When injected, these vaccines can trigger an immune response at the injection site, leading to local skin reactions. These reactions are typically an expected part of the immune response to the vaccine and involve inflammation and immune cell activation.

Overall, the skin toxic effects observed with these treatments result from the intricate interplay between the drugs, the immune system, and the skin's normal physiological processes. Further research is needed to fully understand the underlying pathophysiology of these toxicities and develop strategies to mitigate them while preserving the therapeutic benefits of these treatments.

Histopathological patterns

The histopathological patterns observed in skin lesions associated with targeted therapies, immunotherapies, and cancer vaccines can vary depending on the specific drug, immune response, and underlying mechanisms involved. Here are some common histopathological patterns seen in these skin toxicities:

- **Dermatitis:** Inflammatory changes in the skin, such as lymphocytic infiltrates, can be observed in various skin toxicities. The degree and distribution of inflammation may vary, ranging from mild to severe.
- **Epidermal changes:** Some skin toxicities may exhibit alterations in the epidermis, the outermost layer of the skin. This can include hyperplasia (thickening of the epidermis), acanthosis (epidermal hyperplasia with elongation of rete ridges), or dyskeratosis (abnormal keratinization of cells).
- **Interface dermatitis:** In certain cases, there may be a pattern of interface dermatitis, characterized by inflammation at the junction between the epidermis and dermis. This can manifest as vacuolar degeneration, apoptosis (cell death), or basal cell damage.
- **Spongiosis:** Spongiosis refers to intercellular edema in the epidermis, resulting in separation of keratinocytes. It can be seen in skin toxicities as a consequence of inflammation.
- **Dermal changes:** The dermis, the layer of skin beneath the epidermis, can also show histopathological alterations. These may include perivascular lymphocytic infiltrates, dermal edema, or changes in the collagen or elastic fibers (Figure 2).

It's important to note that these histopathological patterns are not specific to any particular therapy or toxicity. The patterns observed can overlap, and additional features may be present based on the individual's specific condition. A dermatopathologist, a specialized pathologist, can evaluate skin biopsies and provide a more precise diagnosis based on the histopathological findings and clinical context.

Figure 2

What signs and symptoms do these patients have?

Patients experiencing skin toxicities associated with targeted therapies, immunotherapies, and cancer vaccines may present with various signs and symptoms. The specific manifestations can differ depending on the type of therapy, individual patient characteristics, and the severity of the skin toxicity. Here are some common signs and symptoms observed:

- **Rash:** Rash is one of the most frequent skin reactions seen with these treatments. It can range from mild redness or erythema to more severe forms with papules, pustules, or vesicles. The rash may appear localized or affect larger areas of the body.
- **Pruritus:** Itching or pruritus often accompanies skin toxicities. Patients may experience mild to intense itching in the affected areas, leading to discomfort and scratching.
- **Dryness and scaling:** Some individuals may develop dry skin or experience excessive skin scaling, which can cause flaking or peeling of the skin. This can be particularly prominent in certain targeted therapies.
- **Erythema:** Redness or erythema of the skin may occur, either localized or diffusely, as a result of inflammation and increased blood flow to the affected areas.
- **Blistering:** In more severe cases, blistering or bullous lesions may develop. These can be painful and may lead to erosion or ulceration of the skin.
- **Changes in pigmentation:** Certain targeted therapies or immunotherapies may cause alterations in skin pigmentation, leading to darkening or lightening of the affected areas.
- **Pain or discomfort:** Skin toxicities can be associated with varying degrees of pain or discomfort.

This can range from mild tenderness to more intense sensations, such as burning or stinging.

It's important to note that the signs and symptoms can vary greatly among individuals and may be influenced by other factors such as the specific therapy, dose, and duration of treatment. If a patient experiences any concerning skin-related symptoms, it is crucial to consult with their healthcare provider for proper evaluation, management, and potential dose adjustments or treatment modifications (Figure 1).

When these patients are studied, what role does the pathologist play and what is the value of biomarkers and molecular biology?

Figure 3

- **Pathologists:** Pathologists are medical doctors who specialize in diagnosing diseases by examining tissues and cells under a microscope. They play a critical role in diagnosing and characterizing skin toxicities associated with these treatments. By analyzing skin biopsy samples, pathologists can identify the histopathological features, determine the severity and extent of the skin toxicity, and rule out other possible causes of skin lesions. Their expertise aids in providing a precise diagnosis and guiding treatment decisions.
- **Biomarkers:** Biomarkers are measurable indicators that provide information about biological processes, disease progression, or response to treatment. In the context of skin toxicities, biomarkers can help assess the severity of the toxicity, predict the likelihood of developing skin-related adverse events, and monitor the response to therapy. For example, biomarkers such as cytokines, chemokines, or immune cell profiles can be analyzed in blood samples or at the site of the skin toxicity to understand the underlying immune response and guide treatment strategies.
- **Molecular biology:** Molecular biology techniques are employed to investigate the molecular mechanisms underlying skin toxicities. This includes analyzing gene expression patterns, identifying specific molecular targets, or studying the signaling pathways involved. Molecular biology studies can help elucidate the underlying pathophysiology, identify potential drug targets, and develop novel therapeutic strategies to manage or prevent skin toxicities.

The collaboration between pathologists, and researchers specializing in biomarkers and molecular biology is crucial for a comprehensive understanding of skin toxicities associated with these treatments. Their combined expertise helps improve diagnosis, inform treatment decisions, and guide the development of targeted interventions to mitigate or prevent these adverse events.

Genes are involved in skin toxicity

The development of skin toxicity can involve various genes and pathways, and the specific genes implicated can depend on the underlying cause or treatment. However, I can provide some examples of genes that have been associated with skin toxicity in the context of cancer treatment and certain medications:

- **HLA genes:** Human leukocyte antigen (HLA) genes, involved in immune system regulation, have been linked to the development of skin toxicities, particularly in immune-related adverse events (IRAEs) associated with immunotherapies.
- **TPMT gene:** The TPMT (thiopurine S-methyltransferase) gene plays a role in metabolizing certain medications, such as thiopurine drugs. Variants in this gene can affect drug metabolism and increase the risk of skin toxicities in individuals taking these medications.

- **EGFR gene:** The EGFR (epidermal growth factor receptor) gene has been associated with skin toxicities, including acneiform rash, in individuals treated with EGFR inhibitors such as cetuximab or erlotinib.
- **DPD gene:** The DPD (dihydropyrimidine dehydrogenase) gene is involved in the metabolism of fluoropyrimidine-based chemotherapy drugs like 5-fluorouracil (5-FU). Variations in this gene can affect drug metabolism and increase the risk of skin toxicities associated with these medications.
- **IL-17 gene:** Interleukin-17 (IL-17) is involved in the immune response and inflammation. Variations in the IL-17 gene have been associated with increased susceptibility to skin toxicities, such as psoriasis or dermatitis, in certain individuals.

It's important to note that these are just a few examples, and the genetic factors contributing to skin toxicities can be complex and multifactorial. The interplay between genetic factors, treatment-specific mechanisms, and individual patient characteristics influences the development and severity of skin toxicities. Further research is needed to fully understand the genetic markers and pathways involved in different types of skin toxicity.

Relationship between skin toxicity and response to treatment

The presence of cutaneous toxicity does not necessarily reflect a good systemic response to cancer treatment. Cutaneous toxicity, such as skin rashes or other dermatological reactions, can occur as a result of the mechanisms of action of certain therapies, including targeted therapies and immunotherapies. While these toxicities may indicate that the treatment is having an effect on the immune system or specific molecular targets, they do not directly correlate with the overall efficacy or response to cancer treatment.

In some cases, the occurrence of cutaneous toxicity may be associated with a positive treatment response. For example, in certain immunotherapies, the development of immune-related adverse events, including skin toxicities, has been linked to improved outcomes in terms of tumor response or overall survival. This suggests that an activated immune response against the cancer cells may be occurring.

However, it's important to note that cutaneous toxicity can also occur without a concomitant positive systemic response. Some individuals may experience skin toxicities while still having disease progression or a limited response to treatment. Conversely, others may have a positive systemic response without developing significant cutaneous toxicities.

Each patient's response to treatment and the correlation with cutaneous toxicity can vary widely. It is crucial to assess the overall clinical response, including tumor assessments, along with considering the presence and management of cutaneous toxicities. Close communication with the healthcare team is essential to evaluate treatment efficacy and ensure appropriate management of both cutaneous toxicities and the underlying cancer.

Treatment

The treatment of skin toxicities associated with targeted therapies, immunotherapies, and cancer vaccines depends on the specific type and severity of the toxicity. It's important to consult with a healthcare professional to assess the individual's condition and determine the most appropriate management approach. Here are some general strategies and interventions that may be used:

- **Supportive care:** This involves measures to alleviate symptoms and provide comfort. It may include using gentle skincare products, moisturizers, and avoiding harsh soaps or irritants. Maintaining proper hydration and avoiding excessive sun exposure can also be beneficial.
- **Topical treatments:** Depending on the type of skin toxicity, topical medications may be prescribed. These can include corticosteroid creams or ointments to reduce inflammation, antibiotics for bacterial infections, or antifungal agents for fungal infections.
- **Systemic medications:** In more severe cases, systemic medications may be necessary. Corticosteroids or other immunosuppressive drugs may be prescribed to control inflammation or manage immune-related adverse events associated with immunotherapies.
- **Dose modifications:** Adjustments to the dosage or schedule of the cancer treatment may be considered to manage skin toxicities. This can involve temporarily or permanently reducing the dose, extending treatment intervals, or withholding the therapy until the skin toxicity improves.

- **Dermatological interventions:** Dermatologists can provide specialized interventions to manage skin toxicities. These may include procedures such as cryotherapy (freezing), laser therapy, or intralesional injections to target specific skin lesions or manage localized symptoms.
- **Multidisciplinary approach:** In complex cases, a multidisciplinary team, including oncologists, dermatologists, and other specialists, may collaborate to optimize patient care and tailor the treatment plan to individual needs.

It's essential to communicate any skin-related symptoms to the healthcare team promptly. Early intervention and management of skin toxicities can help minimize their impact, improve quality of life, and allow for continued cancer treatment when appropriate.

Prognosis

The prognosis of individuals experiencing cutaneous toxicities associated with targeted therapies, immunotherapies, and cancer vaccines depends on various factors, including the underlying cancer, the severity and extent of the skin toxicity, and the overall response to treatment. It's important to note that the presence of cutaneous toxicity itself does not directly determine the prognosis but rather serves as an indicator of treatment response or adverse events.

In general, the prognosis of individuals undergoing cancer treatment is influenced by factors such as the stage and type of cancer, the overall health of the patient, the specific treatment regimen, and the individual's response to therapy. Cutaneous toxicities can have different implications depending on the context:

- **Positive prognostic implications:** In some cases, the development of cutaneous toxicities, particularly immune-related adverse events in immunotherapies, has been associated with improved treatment outcomes. These skin toxicities may indicate that the immune system is responding to the treatment and may correlate with better overall survival or tumor response rates.
- **Neutral prognostic implications:** Cutaneous toxicities can occur without necessarily affecting the overall prognosis. They may not directly impact the efficacy of cancer treatment or the progression of the underlying disease. In such cases, the prognosis is primarily determined by the cancer itself and the response to treatment beyond the skin toxicities.
- **Negative prognostic implications:** In certain instances, severe or treatment-limiting cutaneous toxicities can impact the ability to continue or tolerate the cancer treatment. In these cases, the management of the toxicities and potential treatment modifications become crucial factors in determining the overall prognosis.

It's important to remember that prognostic assessments should be made in consultation with healthcare professionals who have access to the individual's complete medical history, including the cancer type, stage, treatment plan, and response. They will be best positioned to provide accurate prognostic information and guide appropriate treatment decisions based on the specific circumstances.

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