Curr Probl Cancer 41 (2017) 125–128

Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Cutaneous adverse effects of the immune checkpoint inhibitors

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ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Cutaneous adverse effects
PD-1 inhibitors
CTLA-4 inhibitors
Melanoma

ABSTRACT

The immune checkpoint targeted agents, anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and anti–programed cell death 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) inhibitors are frequently associated with cutaneous side effects that are often dose limiting and can lead to discontinuation of therapy. Ipilimumab, a CTLA-4 inhibitor, is most commonly associated with a morbilliform eruption on the trunk and extremities and pruritus. More severe cutaneous toxicities reported include toxic epidermal necrolysis and severe drug rash with eosinophila and systemic symptoms. Recent case reports of Sweet syndrome and cutaneous sarcoidosis have also recently been described after treatment with ipilimumab. The cutaneous events usually occur early in the course of treatment and are dose dependent. PD-1 inhibitors, nivolumab and pembrolizumab, induce similar but less severe toxicities compared with the CTLA-4 inhibitors. The most common cutaneous adverse events include lichenoid reactions, eczema, vitiligo, and pruritus. Lichenoid oral mucosal lesions located on the tongue, buccal mucosa, lips, or gingivae or located on all of these have also recently been described. The time of onset of the cutaneous events with the PD-1 inhibitors occurs later than that seen with the CTLA-4 inhibitors. Anti–PD-L1

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http://dx.doi.org/10.1016/j.currproblcancer.2016.12.001
0147-0272/

antibodies, such as atezolizumab, have a similar side effect profile compared with the PD-1 inhibitors. Combination of immune checkpoint inhibitors, ipilimumab and nivolumab, has recently been approved for the treatment of advanced melanoma. The combination therapy is associated with a more severe side effect profile compared with the agents used as monotherapy. We discuss the most frequently encountered cutaneous side effects of the immune checkpoint inhibitors and review the recommended management strategies.

The immune checkpoint targeted agents, anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and anti–programed cell death 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) inhibitors, activate the immune system against cancer cells and have been shown to induce dramatic and prolonged clinical responses. However, the nonspecific enhanced immune system response that is promoted by these agents can also lead to a spectrum of side effects. The cutaneous adverse effects frequently encountered with the immune checkpoint inhibitors are often dose limiting and can lead to discontinuation of the therapy.[1] It is, therefore, of utmost importance to have a thorough understanding of the potential cutaneous toxicities so that prompt and appropriate management can be implemented.

CTLA-4 inhibitors

CTLA-4 is a type I membrane protein that is expressed on activated T cells and monocytes, which mediates a local and temporary inhibition of the immune system.[2,3] Ipilimumab, a recombinant human monoclonal antibody that binds to CTLA-4, can abolish the inhibition on the immune system, resulting in sustained immune-mediated antitumor activity.[3-5] The immune-related cutaneous toxicities associated with ipilimumab range from mild pruritus without rash to toxic epidermal necrolysis and severe drug rash with eosinophilia and systemic symptoms.[3,4] The most common presentation is a morbilliform eruption on the trunk and extremities, often associated with generalized pruritus.[3,5,6] The head, palms, and soles are often spared.[5,6] Other less common cutaneous toxicities include prurigo nodularis, lichenoid exanthems, pyoderma gangrenosum-like ulcerations, and vitiligo-like melanoma-associated hypopigmentation, the last of which is associated with improved prognosis.[1,4,7,8] In addition, reports of Sweet syndrome and cutaneous sarcoidosis have recently been described after treatment with ipilimumab for metastatic melanoma.[9-11] The appearance of the cutaneous adverse events occurs early in the course of treatment, typically in the first 3-6 weeks after initiation and appears to be dose dependent.[3,6,12]

The severity of the cutaneous adverse events is graded according to the common toxic effects criteria.[5] Grade I reactions include morbilliform eruptions or erythema without associated symptoms. Grade II reactions include grade I reactions covering $< 50\%$ of body surface area in addition to pruritus or other associated symptoms. Grade III reactions include symptomatic generalized erythroderma or macular, papular, or vesicular eruptions or desquamation covering $\geq 50\%$ of the body surface area. Grade IV reactions include generalized exfoliative dermatitis or ulcerative dermatitis.[5] Most cutaneous adverse effects associated with ipilimumab are grade I or II, with the more serious (grade III and above) events rarely observed.[1,3,4,6] All-grade cutaneous adverse events have been reported in approximately 25% of patients and higher-grade reactions in 2.4%.[6]