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EDITORIAL

Immunotherapy and Coronavirus Disease 2019: Challenges and Possibilities

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Immune checkpoint inhibitors (ICIs), such as anti-programmed cell death-protein 1 (PD-1), anti-programmed death-ligand 1 (PD-L1), and more recently cytotoxic T-lymphocyte–associated antigen 4 monoclonal antibodies, have contributed to significant advances in the management of patients with advanced NSCLC whose disease lacks driver mutations. The use of ICIs leads to an improvement in overall survival (OS) in the first- and second-line settings. Pembrolizumab (anti–PD-1) has an improvement in OS over standard chemotherapy in patients with tumor cell PD-L1 expression of at least 50% or more in the front-line setting. Atezolizumab (anti–PD-L1) has been recently approved by the US Food and Drug Administration for front-line management of advanced cases with PD-L1 expression of at least 50% of tumor cells or more than 10% of infiltrating immune cell in the absence of EGFR or ALK rearrangements. Combination chemoimmunotherapy is an effective strategy in patients with a lower level of tumor PD-L1 expression or those with high tumor burden. Different combination regimens have been tested, including pembrolizumab with chemotherapy and atezolizumab combination with chemotherapy and bevacizumab.[1] Recently, combination of nivolumab and ipilimumab in the first-line setting has been found to have a survival benefit compared with chemotherapy irrespective of PD-L1 expression level.[2]

The immune system is regulated by immune checkpoint molecules, which are stimulatory (e.g., CD28, CD40) and inhibitory (e.g., PD-1, cytotoxic T-lymphocyte–associated antigen 4), that work in harmony to keep T-cell recognition by T-cell receptors and activation in balance between self-tolerance and protection against pathogens. Cancer cells evade immune attack by dysregulating the immune checkpoint system and exploiting PD-1 signals to escape immunity. ICIs remove the tumor inhibitory effects, which result in constitutive activation of T cells (CD4, CD8) with enhanced antitumor activity.[3] Over the past decade, ICIs have become a standard of care in patients with non–oncogene-driven advanced NSCLC at initial presentation.

A major problem in the use of ICIs is the development of immune-related adverse events (irAEs), a class of side effects that can be manifested very early or late with the use of ICIs. The incidence of all grades of irAEs is 16% to 29%.[4] Dermatologic toxicities are one of the common irAEs, and they account for 40% to 50% of irAEs[5] and can appear as early as 4 weeks after the start of immunotherapy. Patients can present with different varieties of skin toxicities. Skin rash and pruritis are the most common dermatologic toxicities and account for 15% to 25% with single-agent ICIs and up to 40% in patients using combination immunotherapy or immunochemotherapy.[6] Vitiligo is observed more frequently in patients with melanoma at a rate of 7.5% to 8.5% and is associated with better OS.[7] Lichenoid eruption presents like lichen planus but with more histiocytic infiltrate and epidermal necrosis.[8] Morbilliform exanthems occur in 15% of patients with anti–PD-1 therapy and resemble drug eruptions. Bullous pemphigoid and severe forms of Stevens-Johnson syndrome/toxic epidermal necrolysis are rare forms that require medical attention and treatment interruptions.[6]

Most dermatologic toxicities are mild and do not require specific therapy or treatment interruption. For grade 1 and 2 toxicities, topical moisturizers and oral antihistamines are recommended with continuation of ICIs. Topical (or low-dose systemic) steroids may be used when signs of inflammation are observed clinically. For patients with grade 3

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toxicity, ICIs should be suspended and intravenous (IV) steroids , (Methyl)prednisolone, should be started with a dose of 1 to 2 mg/kg IV and tapered over a 4-week duration. Dermatology consultation and skin biopsy are recommended. Resuming ICIs is based on risk-to-benefit ratio assuming toxicity grading is down to one or less. For grade 4 toxicity, patients require intensive care monitoring, ICIs should be discontinued permanently, and other alternative anticancer therapy should be considered.[9]

Rolfo et al.[10] report, in this issue of the *Journal of Thoracic Oncology*, the atypical skin manifestations in two patients with stage IV NSCLC on maintenance immunotherapy and recent coronavirus disease 2019 (COVID-19) infection, a pandemic caused by severe acute respiratory syndrome coronavirus 2 infection.

As this pandemic has developed, case reports have been published for different unusual manifestations related to COVID-19, which may resemble certain disease presentations or drug toxicities.

Cutaneous manifestations of COVID-19 have been described in 375 cases during the peak of the pandemic in Spain on the basis of clinical evaluation only. A total of 47% were described as maculopapular with purpura, which resembles erythema elevatum or erythema multiform, 19% as acral erythema with vesicles or pustules, 19% as trunk urticarial lesions, 9% as vesicular eruptions, and 6% as livedo or necrosis with features of vascular occlusive disease.[11]

In the report of Rolfo et al.,[10] the first patient (treated with ipilimumab and nivolumab) developed an urticarial skin rash with skin biopsy results of urticarial vasculitis, macroangiopathic thrombosis, and blood vessel damage; the second patient (on pemetrexed and pembrolizumab maintenance) had features consistent with erythema multiforme. The authors have correlated the skin symptoms to COVID-19 on the basis of the presentation, positive result of severe acute respiratory syndrome coronavirus 2, and presence of inflammatory markers suggestive of severe illness, low level of interleukin-6, and elevated d-dimer. Other points considered were the higher chance of atypical and critical illness in patients with COVID-19 receiving ICIs and the lack of previous skin toxicity in both patients who were on maintenance ICIs for more than a year.

The diagnosis is questionable in both patients! There was no immunohistochemical analysis to determine what type of inflammatory cells infiltrate in the present as patients receiving ICIs can manifest similar cutaneous irAEs with infiltration of CD8 in the dermoepidermal junction and epidermis and keratinocyte apoptosis. In addition, the patients have received steroid, which resulted in controlling the symptoms, similar to what is expected when steroids are used for ICI toxicity.

Rolfo et al.[10] reported an important observation to shed light on possible clinical findings that physician must keep in mind, but direct comparison of the atypical manifestations of COVID-19 and ICI dermatologic toxicity in the reported cases is difficult, and other differential diagnoses are possible, such as drug reactions, viral exanthem, or autoimmune skin disease.

Finally, physicians worldwide encounter unique and difficult issues related to this influenza pandemic. Complications are higher in patients with cancer and those receiving anticancer therapies; hence, more studies and reports are needed to improve our approach when treating patients with immune-modifying agents.

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