Addressing New Diagnostic and Treatment Challenges Associated With a New Age of Cancer Treatment

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A NEW AGE OF CANCER TREATMENT: IMPLICATIONS FOR EMERGENCY CARE

Patients with a cancer-related disease currently represent 4.2% of all emergency department (ED) visits.[1] We can expect this population to increase as the population with a cancer diagnosis in the United States increases from approximately 15 million people to 26 million people by 2040.[2,3] Emergency physicians are well versed in the provision of acute care to patients with cancer and the potential adverse effects of cytotoxic chemotherapy such as neutropenic fever, tumor lysis syndrome, thrombosis, leukostasis, and hyperviscosity syndrome.[4] However, with the rapid development and deployment of new classes of immune-based cancer therapies, the landscape of cancer treatment and its adverse effects is rapidly changing.[5] The article by Majzoub et al[6] in this issue of *Annals* focuses on a new class of such agents, immune checkpoint inhibitors.

Immune checkpoint inhibitors are rapidly being approved by the Food and Drug Administration for a variety of cancer types,[7] including melanoma, non–small cell lung cancer, Hodgkin's lymphoma, and urologic malignancies. Cancer cells can evade the host immune response through complex effects on immune-cell signaling pathways. Checkpoint inhibitors disrupt cell-signaling pathways between T cells and antigen-presenting cells to effectively activate the patient's immune response, thereby preventing cancer cells from evading the patient's immune system.[8,9] Because of this novel mechanism of action, the therapy triggers an immune response to the malignancy. As a result, the expected adverse effects vary significantly from those of cytotoxic chemotherapeutic agents and frequently mimic autoimmune responses, which can affect any organ system and are labeled immune-related adverse events.[10] The clinical picture is thus similar to one of autoimmune disease rather than immunosuppression.[11] Additionally, symptoms can manifest weeks to months after treatment is initiated or completed, complicating the identification of treatment-related adverse effects. Identifying immune-related adverse events requires emergency providers to have a high degree of clinical suspicion and to obtain a thorough clinical history that includes current and past oncologic treatments.

Review articles on immune-related adverse events targeting emergency providers have recently been published and warrant study.[11,12] The article by Majzoub et al[6] provides the first look at patients with specific immune-related adverse events and presenting to the ED of a large cancer center. They found that a quarter of ED patients receiving immune checkpoint inhibitors presented with an immune-related adverse event; the most common were consistent with those found in other settings, including diarrhea or colitis, pneumonitis, and dermatitis. Rarer immune-related adverse events were also found, including potentially life-threatening hypophysitis, myocarditis, and vasculitis.

The potential presence of immune-related adverse events necessitates a new approach to the diagnosis, treatment, and disposition of patients receiving immune checkpoint inhibitors and presenting to the ED. For example, no longer can dyspnea be considered most likely caused by pneumonia or pulmonary embolus; the possibility of immune-mediated pneumonitis must be considered as well. Likewise, for patients with chest pain, myocarditis and pericarditis must be considered; and for patients with headache, hypophysitis. Traditional laboratory-value red flags, such as neutropenia, are not likely to be present in these patients. Education in regard to these new therapeutics is essential for all emergency providers and should be prioritized. In an effort to aid in the identification of immune-related adverse events and to improve care coordination, many cancer centers are

providing patients with wallet cards that list their current medications and potential adverse effects requiring monitoring.[13] Because this tool could greatly improve the acute care of patients receiving immune checkpoint inhibitors, emergency providers should establish a dialogue with their oncologist colleagues to advocate such cards to streamline communication.

Equally challenging to the identification of immune-related adverse events is determining the next best course of treatment. To address this question, the American Society of Clinical Oncology published comprehensive guidelines in February 2018 targeting an audience that includes emergency medicine providers.[14] These guidelines provide diagnostic definitions and treatment recommendations for immune-related adverse events according to the severity of the patient's presentation. The critical point for the emergency physician is that the treatment and disposition decisions should be made in conjunction with an oncologist. Treatment and disposition depend on the immune-related adverse event type, and severity and can range from discontinuation of therapy to administration of oral or intravenous systemic steroids. Because steroids may inhibit the immune checkpoint inhibitor's mechanism of action, they should be administered only in life-threatening situations or in consultation with the patient's primary oncologist and the American Society of Clinical Oncology guidelines.

Combination immune checkpoint inhibitor therapies are also becoming increasingly common among patients with melanoma and non–small cell lung cancer.[9] Combination immune checkpoint inhibitor therapy has been associated with higher rates of immune-related adverse events than single-agent immune checkpoint inhibitor regimens.[15] Caring for a patient presenting to the ED who is receiving a combination of multiple immune checkpoint inhibitors should prompt the emergency provider to consider immune-related adverse events as potential causes for suspicion symptoms.

In addition to immune checkpoint inhibitors,[16] a second class of targeted immune-based therapy has been developed, chimeric antigen receptor T-cell therapy, which engineers the patient's own T cells to recognize antigens on tumor cells.[17] Patients receiving this class of therapy also present with immune-related adverse events, and although the immune-related adverse events associated with chimeric antigen receptor T-cell therapy can be catastrophic (eg, encephalopathy, coma, fulminant hemophagocytic lymphohistiocytosis) and tend to occur closer to treatment initiation, similar considerations and recommendations apply. Nonspecific immunotherapies such as interferons[18] and interleukins[19] are also being used. Patients receiving these therapies tend to present with nonspecific flulike symptoms.[20,21] For all patients receiving immunotherapy, a thorough medical history, high index of suspicion, and close communication with oncologists are essential to provide quality care.

The provision of acute care for patients with cancer is increasingly becoming a major component of the care provided in the ED. In the new age of immune-based cancer treatments, emergency providers play an essential role in identifying subtle symptoms of immune-related adverse events as potential indicators of catastrophic treatment adverse effects. There exists an urgent need to change the approach of emergency providers to these patients, provide continuing education on immune-related adverse events, and update the ED-based cancer research agenda[22] to include immune therapies and immune-related adverse events. We are encouraged that emergency providers are taking the lead to further identify and address this need through new and innovative research[6] and research collaborations, such as the Comprehensive Oncologic Emergencies Research Network.[23] However, it is crucial that we look beyond the ED and collaborate with our oncologist colleagues to provide the best-coordinated care possible.

In conclusion, the rapidly changing cancer treatment landscape poses a new and daunting challenge that requires emergency providers to stay informed and vigilant in the nuanced presentations of immune-related adverse events. Emergency provider engagement with their local oncologists, continuing education opportunities on the topic, and the revision of the emergency research agenda priorities are essential in addressing this challenge.

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REFERENCES

1. Rivera DR, Gallicchio L, Brown J, et al. Trends in adult cancer-related emergency department utilization: an analysis of data from the Nationwide Emergency Department Sample. *JAMA Oncol*. 2017;3:e172450.
2. Howlader N, Noone A, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD: SEER; 2016.
3. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016;25:1029-1036.
4. Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: pathophysiology, presentation, diagnosis, and treatment. *CA Cancer J Clin*. 2011;61:287-314.
5. O'Connor JM, Fessele KL, Steiner J, et al. Speed of adoption of immune checkpoint inhibitors of programmed cell death 1 protein and comparison of patient ages in clinical practice vs pivotal clinical trials. *JAMA Oncol*. 2018;4:e180798.
6. Majzoub I, Qdaisat A, Thein KZ, et al. Adverse effects of immune checkpoint therapy in cancer patients visiting the emergency department of a comprehensive cancer center. *Ann Emerg Med*. 2018; http://doi.org/10.1016/j.annemergmed.2018.04.019.
7. UpToDate. Patient selection criteria and toxicities associated with checkpoint inhibitor immunotherapy. Available at: https://www.uptodate.com/contents/patient-selection-criteria-and-toxicities-associated-with-checkpoint-inhibitor-immunotherapy. Accessed June 11, 2018.
8. Dine J, Gordon R, Shames Y, et al. Immune checkpoint inhibitors: an innovation in immunotherapy for the treatment and management of patients with cancer. *Asia Pac J Oncol Nurs*. 2017;4:127-135.
9. Salama AK, Moschos SJ. Next steps in immuno-oncology: enhancing antitumor effects through appropriate patient selection and rationally designed combination strategies. *Ann Oncol*. 2017;28:57-74.
10. Bayer V, Amaya B, Baniewicz D, et al. Cancer immunotherapy: an evidence-based overview and implications for practice. *Clin J Oncol Nurs*. 2017;21:13-21.
11. Pallin DJ, Baugh CW, Postow MA, et al. Immune-related adverse events in cancer patients. *Acad Emerg Med*. 2018;25:819-827.
12. Simmons D, Lang E. The most recent oncologic emergency: what emergency physicians need to know about the potential complications of immune checkpoint inhibitors. *Cureus*. 2017;9:e1774.
13. Rubin KM. Understanding immune checkpoint inhibitors for effective patient care. *Clin J Oncol Nurs*. 2015;19:709-717.
14. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1714-1768.
15. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
16. Burugu S, Dancsok AR, Nielsen TO. Emerging targets in cancer immunotherapy. *Semin Cancer Biol*. 2017; http://doi.org/10.1016/j.semcancer.2017.10.001.
17. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci Transl Med*. 2011;3; 95ra73.
18. Corrales L, Gajewski TF. Molecular pathways: targeting the stimulator of interferon genes (STING) in the immunotherapy of cancer. *Clin Cancer Res*. 2015;21:4774-4779.
19. Anestakis D, Petanidis S, Kalyvas S, et al. Mechanisms and applications of interleukins in cancer immunotherapy. *Int J Mol Sci*. 2015;16:1691-1710.
20. Dhingra K, Talpaz M, Dhingra HM, et al. A phase I trial of recombinant alpha-2a interferon (roferon-A) with weekly cisplatinum. *Invest New Drugs*. 1991;9:37-39.
21. Schwartz RN, Stover L, Dutcher JP. Managing toxicities of high-dose interleukin-2. *Oncology (Williston Park)*. 2002;16:11-20.
22. Brown J, Grudzen C, Kyriacou DN, et al. The emergency care of patients with cancer: setting the research agenda. *Ann Emerg Med*. 2016;68:706-711.
23. Greene J. CONCERN for cancer: new National Institutes of Health network to focus on cancer patients in the emergency department. *Ann Emerg Med*. 2015;66:13a-15a.