## New Immunotherapy Revolutionizes Cancer Care, but Guess Where Adverse Events End Up?

## BY DUSTIN BALLARD, MD, & DAVID VINSON, MD

69-year-old man with a history of cancer presented to our ED on day four of taking Ceftin for pneumonia with a fever of 102.5°F and shortness of breath. He had a history of non-small cell lung cancer after a wedge resection and hepatocellular carcinoma after a hepatectomy. His chest film was read as "patchy airspace disease over mid- and lower lung without improvement from prior," and he was worked up, treated, and admitted for severe sepsis. Sounds like a fairly bread-andbutter emergency department case, right?

Of course, there was a twist, which emerged after a CT of the chest and bronchoscopy demonstrated diffuse ground glass opacity and tracheobronchitis, findings that resolved with high-dose prednisone. The diagnosis was not pneumonia but pneumonitis, a complication of the patient's cancer treatment—pembrolizumab (Keytruda), last administered several months before presentation.

Pembrolizumab is one of the new-generation cancer treatments that deploys the patient's immune system against cancer cells by removing the malignant cells' ability to disguise themselves rather than killing them directly. These checkpoint inhibitors are revolutionizing oncologic treatment, but are not a risk-free panacea. We all know where these patients are likely to be seen and evaluated when severe side effects emerge.

## Be on the Lookout

Immunotherapy complications have been receiving some attention from scientific journals as well as the lav press this year. Actual data on adverse effect risk, especially for those with a delayed presentation like our patient, remain limited. An Annals of Emergency Medicine study gives us our best sense of the prevalence and nature of side effects in practice, albeit with data from a single and specialized ED setting. (Ann Emerg Med 2018 Jun 4; doi: 10.1016/j.annemergmed.2018.04.019.)

The authors retrospectively reviewed records of patients over age 17 on immune checkpoint therapy who visited the University of Texas MD Anderson Cancer Center ED between March 2011 and March 2016. The study's primary goal was to characterize the nature and mortality risks of any adverse reactions to one or more of three immunotherapy medications (pembrolizumab, nivolumab [Opdivo], ipilimumab [Vervoy]).

The study identified 1,026 visits among 628 patients, and 257 visits (25%) were related to one or more adverse effects. The list of these starts with diarrhea (12.7%) and continues in descending order of frequency: colitis, pneumonitis, dermatitis, hypophysitis, hepatitis, thyroiditis, pancreatitis, adrenalitis, mvocarditis,

and vasculitis. Pneumonitis posed the greatest survival risk (hazard ratio 1.72 [95% CI 1.03-2.87] in multivariable Cox regression modeling), and multiple drug therapy made certain specific reactions more likely (e.g., thyroiditis and hypophysitis) than single-drug therapy. We EPs should presume that any patient with active cancer could be on these medications, and we should be on the lookout for their adverse reactions.

Fortunately, recent articles in Academic Emergency Medicine and Cureus addressed the physiology, grading, and treatment of checkpoint inhibitor therapies. (Acad Emerg Med 2018 May 5; doi: 10.1111/ acem.13443; Cureus 2017;9[10]: e1774; http://bit.ly/2L5zgOk.) The American Society of Clinical Oncology and the National Comprehensive Cancer Network also published guidelines on these. (J Clin Oncol 2018;36[17]:1714; http://bit. ly/2L1RgZV.) Most important are the grading recommendations (1-4) with

## **Checkpoint Inhibitors in Rhyme**

By David Vinson, MD

These meds can enhance our immunity Causing far greater distress By promoting a state of disunity— Releasing the brakes, Raises the stakes,

With no guarantee of impunity.

The system is on the attack Indifferent to who it might sack: Cancer? True: But other cells too. Will find themselves on the rack.

Events from these agents immune Need not occur anytime soon; Post-med delays Can be hundreds of days— Beware the long honeymoon.

It's clear when the gut gets affected: Diarrhea and pain are expected; When colitis brews Bleeding ensues-Deficits may need to be corrected.

These meds can the dermis derange With a breadth that's remarkably strange: Itch or rash Or vitiligo splash— One end of severity's range.

Are conditions like S.J.S. And necrolysis-Also a crisis Requiring more treatment finesse.

The endocrine effects are elusive: The symptoms are far from exclusive; Headache, malaise Suspicions should raise— Only testing here is conclusive.

Fever, anorexia, pneumonitis, Arthralgia, as well as nephritis-The list is long Of what can go wrong: From vision to myocarditis.

The first step is rule out infection And consider cancer progression. Don't go this alone-Get onc on the phone; We need their enlightened impression.

To curtail the over-expression Of a system that's moved to aggression— On steroids rely The response rate is high— The treatment? Immunosuppression.

sensible management ramifications. The skinny is that minor toxicities (Grade 1) can usually be closely monitored without stopping treatment, but Grade 2 and above require immunosuppression (corticosteroid first-line, infliximab second-line) and holding or suspending immunotherapy altogether.

The test with this practicechanger will be in the awareness and recall. We must recognize the at-risk patient and remember that delayed symptoms can be common. We penned a limerick to help us remember to add checkpoint inhibitors to the differential diagnosis checklist. (See sidebar.) EMN

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