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Study details incidence and timing of immunotherapy-related fatalities

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Vanderbilt-Ingram Cancer Center researchers have answered questions about the incidence and timing of rare but sometimes fatal reactions to the most widely prescribed class of immunotherapies.

Their research, which appeared Sept. 13 in *JAMA Oncology*, is the largest evaluation of fatal immune checkpoint inhibitor toxicities published to date. They determined that although these severe events can happen, the risks are "within or well below" fatality rates for more common cancer treatments, including chemotherapy, stem cell transplants and complex cancer surgeries.

When fatal reactions did occur, they tended to happen early after starting treatment, on average 15-40 days, depending upon the type of immune checkpoint inhibitor. Their study further characterized the fatal toxicities and timing of reaction by type of cancer and specific drug.

"These drugs are quite transformative," said Douglas Johnson, MD, MSCI, senior author of the article. "The benefits outweigh the risks, but patients and doctors should be aware of their toxicities. These side effects can be quite severe, and they are something that we really need to pay attention to."

The team sorted through more than 16 million adverse drug reaction reports in a World Health Organization (WHO) database searching for those related to immune checkpoint inhibitors. They also reviewed the records from seven academic centers, including Vanderbilt, that have

been at the forefront of immunotherapy research. Additionally, they conducted a meta-analysis of published trials for the drugs.

Checkpoint inhibitors unleash the immune system to attack cancer, but they may also spur an attack on organs, including the heart, lungs, liver and colon. Steroids are prescribed to relieve the resulting inflammation: myocarditis, pneumonitis, hepatitis and colitis, and are usually extremely effective. Timely treatment with steroids is crucial, Johnson said.

"Some of the patients who died had a long delay before they received steroids," Johnson said. "In some cases, the patient didn't call in to report their symptoms or experienced a very unusual presentation that was difficult to diagnose."

The data also showed that older patients were more prone to experience fatal toxicities, although the occurrence was still rare.

"We don't necessarily think that older patients have more side effects, but when they do have toxicities, they can potentially have more complications," Johnson said.

The team found 613 fatal immune checkpoint inhibitor toxicities within the more than 16 million reports in the WHO pharmacovigilance database (Vigilyze) from 2009 to 2018. Myocarditis (inflammation of the heart) had the highest fatality rate, as nearly 40 percent of patients with this side effect died.

The review of records from the seven academic centers revealed a 0.6 percent fatality rate. The meta-analysis of data from 112 clinical trials showed a fatality death rate ranging from 0.36 percent to 1.23 percent, depending upon the specific type of immune checkpoint inhibitor.

The study notes that this range is "dramatically lower than the near 100

percent fatality rate for metastatic solid tumors." The U.S. Food and Drug Administration has at this point in time approved immune checkpoint inhibitors for 13 different types of metastatic cancers.

"We have clinics full of patients now who received these treatments who are alive today because they responded to these treatments," Johnson said.

Provided by Vanderbilt University Medical Center

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