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Side Effects From Certain Immunotherapies May Be Higher Than Initially Reported

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Expert Perspective

“Immunotherapy checkpoint inhibitors are extending the lives of many cancer patients, but as with any new therapy, their use is not without risk of side effects. We've only been using these therapies for a few years, so this new analysis gives us more information on the prevalence of these side effects in patients as the therapies gain wider use,” said Joe Rotella, MD, MBA, HMDC, FAAHPM, Member, 2018 Palliative and Supportive Care in Oncology Symposium.

ALEXANDRIA, Va. – An analysis of nearly 2,800 people with non-small cell lung cancer (NSCLC) who received the immune checkpoint inhibitors nivolumab (Opdivo), pembrolizumab (Keytruda), or atezolizumab (Tecentriq) found that unexpected medical problems, known as adverse events, may be more common than reported in the initial trials that led to the approval of these therapies. These findings will be presented at the upcoming 2018 Palliative and Supportive Care in Oncology Symposium in San Diego, California.

“Immunotherapy continues to be well tolerated, and severe side effects are less frequent than those seen with conventional chemotherapy. Still, immunotherapy can, in rare occasions, cause other serious medical problems,” said senior study author Elizabeth Jane Cathcart-Rake, MD, a fellow at the Mayo Clinic, Rochester, Minnesota. “It's important to understand the full extent of cancer treatments’ side effects, and patients and providers
should be aware that it can take a while to fully assess them for newer therapies.”

As an example based on a different type of therapy, Dr. Cathcart-Rake cited the initial clinical trial results of aromatase inhibitors for breast cancer which reported joint pain in about 8% of patients. Current findings, based on patient-reported outcomes and more comprehensive analyses over the past two decades, show that about 50% of patients taking aromatase inhibitors report joint pain.

**About the Study**

The researchers reviewed claims data from a large insurance database that listed adverse events due to immunotherapy. The database, OptumLabs Data Warehouse, was co-founded by the Mayo Clinic in 2012 and includes de-identified clinical data from more than 150 million people in the United States. The investigators determined if people received the PD-1 or PD-L1 immunotherapy checkpoint inhibitors nivolumab, pembrolizumab, or atezolizumab between 2015 and 2017 and then looked at the frequency of immune-related adverse events. Most patients received standard forms of chemotherapy prior to their immunotherapy treatment.

“We believe that our study is the first to look at adverse events based on claims data, which gives a much broader, population-based perspective on outcomes than a single trial,” said Dr. Cathcart-Rake. “While there have been studies comparing data from multiple trials, our approach includes a comprehensive look at outcomes for most insured patients.”

The researchers were not able to account for people who do not have insurance, a potential limitation of the study.

**Key Findings**

The most common immune-related adverse outcome, hypothyroidism, occurred in 9.2% of patients. This was not unexpected as the thyroid is sensitive to immune stimuli. Other side effects, such as anemia, occurred in 5.7% of patients and acute kidney injury occurred in 2.8% of patients. Gastrointestinal and cardiac events were relatively rare.

Analyses of the data are ongoing so that researchers can obtain a better understanding of the absolute differences between trial reported toxicities and those seen in the population at
According to the authors, only about 14% of trials report adverse events at the time of publication. However, one trial, KEYNOTE-24, which compared pembrolizumab vs. chemotherapy, allowed the authors to compare initial results with population-based data. KEYNOTE-24 reported that 0.6% of patients had hypophysitis, a rare condition involving acute or chronic inflammation of the pituitary gland, while this analysis found that 2.4% of patients experienced hypophysitis.

Next Steps

As a next step, the researchers may look at the timing of autoimmune side effects, which can be found in insurance-provider databases. If clinicians knew when side effects were most likely to occur, they could intervene in a timely manner.

2018 Palliative and Supportive Care in Oncology Symposium News Planning Team

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View the disclosures for the News Planning Team.

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2018 Palliative and Supportive Care in Oncology Symposium: Presentation Information
Abstract ID: 236121

Title: Immunotherapy-related toxicities: More common than originally reported?

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Topic Selection: Symptom Biology, Assessment, and Management - Symptom Biology, Assessment, and Management

Background: Population level data regarding incidence of immune-related adverse events (irAE) is lacking. This study evaluated the frequency of irAEs among a large population of patients with non-small cell lung cancer (NSCLC) who received immune checkpoint inhibitors.

Methods: Administrative claims data from a large U.S. commercial insurance database (OptumLabs Data Warehouse) were used to retrospectively identify patients with NSCLC who received PD-1 or PD-L1 inhibitors between January 1, 2015 to December 31, 2017. The frequencies of irAEs were reported, identified by having a new medical claim with a corresponding ICD-9 or ICD-10 code during the time period in which the patient was on immunotherapy.
**Results:** Of 2,798 patients with NSCLC (median age at PD-(L)1 initiation: 69 years, interquartile range: 60-75, 1,558 male [55.7%], 1,240 [44.3%] female), 1,998 (71.4%) received nivolumab, 699 (25.0%) received pembrolizumab, and 101 (3.6%) received atezolizumab. Most patients (1,463, 52.3%) received a PD-(L)1 inhibitor as second line therapy; the majority of patients (744) received alkylating agents and antimetabolites prior to receiving PD-(L)1 therapy. See Table 1 for frequencies of irAEs.

**Conclusions:** The current study suggests that the frequencies of some irAEs related to immune checkpoint inhibitor therapies may be higher than those which were reported in the initial trials that led to the FDA approvals for immunotherapies. For example, hypophysitis was noted to occur in 0.6% of patients in the KEYNOTE-024 trial but was identified in 2.4% of patients in this large cohort. Real world data may refine provider and patient expectations for outcomes beyond what is observed in clinical trials.

Frequencies of irAEs.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Toxicity</th>
<th>Frequency</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism</td>
<td>257</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Hypophysitis</td>
<td>67</td>
<td>2.4</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
<td>160</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Acute kidney injury</td>
<td>78</td>
<td>2.8</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td>49</td>
<td>1.8</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neuritis</td>
<td>40</td>
<td>1.4</td>
</tr>
</tbody>
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**About ASCO:** Founded in 1964, the American Society of Clinical Oncology, Inc. (ASCO®) is committed to making a world of difference in cancer care. As the world’s leading organization of its kind, ASCO represents nearly 45,000 oncology professionals who care for people living with cancer. Through research, education, and promotion of the highest-quality patient care, ASCO works to conquer cancer and create a world where cancer is prevented or cured, and every survivor is healthy. ASCO is supported by its affiliate organization, the Conquer Cancer Foundation. Learn more at www.ASCO.org, explore patient education resources at www.Cancer.Net, and follow us on Facebook, Twitter, LinkedIn, and YouTube.

**About the American Academy of Hospice and Palliative Medicine:**

The American Academy of Hospice and Palliative Medicine’s (AAHPM) is the professional organization dedicated to advancing hospice and palliative care and improving the care of patients with serious illness. Our activities focus on professional education and training, development of a specialist workforce, support for clinical practice standards, research, and public policy advocacy.

**About the American Society for Radiation Oncology:**
The American Society for Radiation Oncology (ASTRO) is the premier radiation oncology society in the world, with more than 10,000 members who are physicians, nurses, biologist, physicists, radiation therapists, dosimetrist and other health care professionals that specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, the Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy standards, advancement of science and research, and advocacy. ASTRO publishes three medical journals, *International Journal of Radiation Oncology, Biology, Physics*, *Practical Radiation Oncology*, and *Advances in Radiation Oncology*, developed and maintains an extensive patient website; and created the Radiation Oncology Institute, a non-profit foundation to support research and education efforts around the world that enhance and confirm the critical role of radiation therapy in improving cancer treatment.

**About the Multinational Association of Supportive Care in Cancer:**
The Multinational Association of Supportive Care in Cancer (MASCC) is an international, multidisciplinary organization with members from six continents and nearly 70 countries. It operates in collaboration with the International Society of Oral Oncology (ISOO). Founded in 1990, MASCC is dedicated to research and education in all areas of supportive care for patients with cancer, regardless of the stage of the disease. MASCC promotes professional expertise in supportive care through research and the scientific exchange of ideas. A focus on supportive care leads to better treatment outcomes and greater quality of life for people with cancer.