

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Identifying and Addressing the Toxicity of Checkpoint Inhibitors in Lung Cancer



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H&O What are the toxicities that occur with various types of immunotherapy, and how common are they?

JB Checkpoint inhibitors can produce immune-related side effects in any organ or system of the body: the skin, gastrointestinal tract, endocrine glands, liver, nervous system, and pulmonary system. They can cause inflammatory conditions such as colitis, hypophysitis, nephritis, and uveitis—anything that ends in *-itis*. The most common side effects, however, are fatigue, rash, mild nausea, and decreased appetite, all of which are relatively easy for the patient to tolerate and the physician to treat. We also commonly see elevated or decreased thyroid hormone levels, which we are able to treat.

Approximately 70% of patients receiving a checkpoint inhibitor experience some type of side effect. Only 10% of patients experience a grade 3 or 4 side effect, however. Those percentages are pretty consistent across all of the checkpoint inhibitors. It is important to remember that clinical trials have shown that checkpoint inhibitors produce less toxicity than does single-agent chemotherapy. Side effects that cause death or require discontinuation of the checkpoint inhibitor are rare.

H&O How do the various checkpoint inhibitors compare with one another in terms of toxicity?

JB Our data on that question come mostly from trials in melanoma, in which we have seen much less toxicity and colitis with the anti-programmed death 1/programmed

death ligand 1 (anti-PD-1/PD-L1) agents than with the anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) agents. The US Food and Drug Administration (FDA) has approved the anti-CTLA-4 agent ipilimumab (Yervoy, Bristol-Myers Squibb) and the anti-PD-1/PD-L1 agents pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb).

H&O Are there any rare side effects of checkpoint inhibitors that physicians may not be aware of?

JB A couple of examples of less well-recognized side effects are myasthenia gravis and myocarditis. Physicians need to ask themselves whether any symptom the patient is experiencing—headache, fatigue—might be related to the immune system. It is also important to remember that side effects may occur months after an agent has been discontinued because the checkpoint inhibitor can continue to affect the patient's body for a long time.

H&O What can physicians do to reduce the risk of toxicity with these agents?

JB Right now, we do not have anything we can give patients prophylactically to reduce the risk of side effects. All we can do is screen patients appropriately and not administer checkpoint inhibitors to those who have autoimmune diseases. Someone who has an overactive immune system is a poor candidate for this type of drug because it can exacerbate the symptoms of the autoimmune disease.

If severe side effects occur, we need to stop administering the agent, treat the patient with corticosteroids, and determine the precise cause of the reaction. For example, if we see abnormal results of a patient's liver function test, we are very aggressive about doing a liver biopsy to detect hepatitis because this is an uncommon side effect of checkpoint inhibitors. If we see a patient with shortness of breath, we also need to investigate thoroughly. In such a case, we need to partner with a pulmonologist to rule out pneumonitis, and with an infectious disease specialist to rule out an infection.

H&O What about patients with an unconfirmed diagnosis of an autoimmune disorder?

JB If there is any question about a patient's diagnosis, we need to obtain the medical records if at all possible. We certainly see a lot of patients who were told at one time that they had rheumatoid arthritis based on the results of a laboratory test but who did not have classic symptoms of the disease. The oncologist could consider trying checkpoint inhibitors in such patients, with the understanding that the syndrome might recur. In contrast, checkpoint inhibitors should not be used in a patient with ongoing symptoms despite treatment, or with a clear diagnosis of an autoimmune disorder, such as rheumatoid arthritis, that requires active treatment.

I do not have a problem with using checkpoint inhibitors in people who have Hashimoto thyroiditis. People with type 1 diabetes also can receive checkpoint inhibitors. For patients with bowel issues, it is important to determine whether the problem is an inflammatory bowel disease—which would preclude the use of checkpoint inhibitors—or a noninflammatory syndrome. In such instances, I would look for documentation of a colon biopsy.

H&O What should physicians do to detect toxicity early in patients taking checkpoint inhibitors?

JB First, we need to ask about side effects every time these patients come in for treatment. Second, we need to educate them about which side effects to watch for. Patients need to understand that if they experience diarrhea, they should call their doctor's office right away and discuss with the staff whether they need to come in, rather than assume that they have a routine gastrointestinal illness. The office staff needs proper training in order to handle these calls. Everyone, including the patient's internist and any other health care professionals who may be providing treatment, must be aware that the patient is taking a checkpoint inhibitor and that it may be causing side effects. During the stomach flu season, there is a

big difference between a patient who is on a checkpoint inhibitor and a typical patient presenting to the emergency department with diarrhea, nausea, and vomiting.

H&O What laboratory tests should be ordered routinely in patients taking checkpoint inhibitors?

JB Some physicians monitor the levels of amylase and lipase because pancreatitis can develop, and other physicians advocate following the levels of cortisol and adrenocorticotropic hormone; however, it is mainly the thyroid hormone levels that need to be monitored. Thyroid function should be tested every 6 weeks, or more often in patients who have symptoms of thyroiditis.

H&O How should toxicities be evaluated and treated?

JB For patients with low-grade side effects, the treatment obviously depends on the side effect. Physicians can refer to the recommendations that have been laid out by the drugs' manufacturers, such as the Immune-Mediated Adverse Reactions Management Guide for ipilimumab. Patients whose side effects are low grade often can continue to receive the agent. Patients who have grade 2 or higher toxicities affecting the liver, lungs, or colon usually benefit from stopping checkpoint inhibitor treatment and starting corticosteroids.

If the side effects are not controlled by corticosteroids, patients need to receive more intense therapy with an agent such as infliximab (Remicade, Janssen Biotech) or mycophenolate.

H&O Under what circumstances should immunotherapy be discontinued?

JB Checkpoint inhibitors should be discontinued permanently for any toxicity that is grade 3 or higher and does not abate or takes a long time to abate with a corticosteroid. Toxicities may take a long time to abate, but eventually they do unless the thyroid gland, pituitary gland, adrenal glands, or pancreas has been damaged. We typically recommend that patients stay on corticosteroids for at least 6 weeks, with a slow taper during that time. Patients whose disease flares when the corticosteroid dose is decreased require longer tapers.

H&O When patients are removed from the therapy, does the benefit tend to continue?

JB Yes; we have had many patients who have stopped treatment because of side effects or other reasons and whose disease has not recurred.

H&O Are any checkpoint inhibitors in development that might be less toxic than the ones currently in use?

JB Many checkpoint inhibitors are in development, but at this point we do not know what to expect regarding toxicity.

H&O Are you concerned about an increased risk for toxicity with the use of checkpoint inhibitors in combination and in higher doses?

JB Yes, we are concerned about additive toxicity rates with the combinations, which we have seen in studies of melanoma and in early studies of lung cancer. The lung cancer studies include CheckMate 012 (Study of Nivolumab in Combination With Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects With Stage IIIB/IV Non-Small Cell Lung Cancer), which was presented by Dr Nayer Rizvi at the 16th World Conference on Lung Cancer; MK-3475-021/KEYNOTE-021 (A Study of Pembrolizumab in Combination With Chemotherapy or Immunotherapy in Participants With Lung Cancer), a study of pembrolizumab and ipilimumab in non-small cell lung cancer presented by Dr Amita Patnaik at the American Society of Clinical Oncology annual meeting in 2015; and a study of tremelimumab and MEDI4736 that Dr Rizvi presented at the Society for Immunotherapy of Cancer (SITC) 2015 meeting. Patients demonstrated higher response rates with all of these agents but also higher rates of side effects. By adjusting doses or schedules, however, we may be able to mitigate some of the side effects.

H&O Any final thoughts?

JB Although we are discussing side effects, the truth is that these agents are very easy for most people to tolerate. Physicians and patients do need to be aware of the side effects, however, and physicians should have a low threshold for evaluating symptoms. If patients have skin lesions, they may require a biopsy. If symptoms of arthritis develop, they may need to see a rheumatologist. Oncologists are not used to encountering autoimmune reactions, and we need to work hand in hand with experts who manage these types of issues on a routine basis in people who do not have cancer.

Suggested Readings

Antonia SJ, Goldberg SB, Balmanoukian AS, et al. Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC [ASCO abstract 3014]. *J Clin Oncol*. 2015;33(15)(suppl).

Bristol-Myers Squibb. Immune-mediated adverse reactions management guide. Yervoy. <http://www.hcp.yervoy.com/a/resources-support>. Revised October 2015.

Keytruda [package insert]. Whitehouse Station, NJ: Merck; 2015.

Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2016.

Patnaik A, Socinski MA, Gubens MA, et al. Phase 1 study of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D [ASCO abstract 8011]. *J Clin Oncol*. 2015;33(15)(suppl).

Rizvi N, Chafit J, Balmanoukian A, et al. Tumor response from durvalumab (MEDI4736) + tremelimumab treatment in patients with advanced non-small cell lung cancer (NSCLC) is observed regardless of PD-L1 status. Presented at: Society for Immunotherapy of Cancer 2015; November 4-8, 2015; National Harbor, Maryland. Abstract P477.

Rizvi N, Gettinger SN, Goldman JW, et al. Safety and efficacy of first-line nivolumab (NIVO; anti-programmed death-1 [PD-1]) and ipilimumab in non-small cell lung cancer (NSCLC). Presented at: 16th World Conference on Lung Cancer; September 6-9, 2015; Denver, Colorado. Oral abstract 02.05.