What Are the Potential Side Effects? (An Immunotherapy Primer for Patients, Pt. 4)

While immunotherapies are sometimes considered to be nontoxic or minimally toxic alternatives to standard treatments such as chemotherapy, it is more appropriate to recognize that they can be exceptionally well tolerated but can also be associated with a distinct constellation of potential immune-mediated side effects that range from trivial to serious and potentially life-threatening (Figure 3). Serious side effects are seen in less than 10% of patients, and typically emerge an average of 6 to 12 weeks after the start of treatment; however, they may also start within days of the first dose, many months into treatment, or sometimes even after discontinuation of therapy. The risk of side effects increases with higher doses, and overall seems to increase with cumulative exposure. Moreover, as immunotherapies are being tested in combination, side effects tend to be additive.

The more common adverse effects are related to GI inflammation, which can be as minor as slight irritation or as severe as colitis (inflammation of the colon), potentially even leading to perforation of the bowel. Symptoms can include bloating, cramps, diarrhea, bloody stools, abdominal pain, and nausea. A medical evaluation includes reporting on the frequency and volume of diarrhea, potentially a stool sample to check for infection, imaging that may include an abdominal ultrasound and/or CT scan, and possibly direct visualization with a colonoscopy. Treatment often includes hydration when needed, anti-spasmodic medication such as dicyclomine (Bentyl), anti-diarrheal medications, and potentially steroids or the medication infliximab (Remicade).

Thyroiditis, or inflammation of the thyroid, is another common side effect, and it may lead to excessively high activity (hyperthyroidism) or low activity (hypothyroidism). Because the thyroid gland regulates metabolism, growth, and temperature control, typical symptoms of hyperthyroidism include weight loss, a fast heart rate, irritability, diarrhea, and feeling warm most of the time, while the symptoms of hypothyroidism often include weight gain, fatigue, dry skin, constipation, and feeling cold. It is common for hyperthyroidism to later transition to a normal or hypothyroid state. Blood tests can determine the function of the thyroid. Hyperthyroidism is generally treated with “beta blockers,” blood pressure medications that slow the heart rate, combined with symptomatic management of patient’s symptoms. Hypothyroidism is readily treated with thyroid hormone replacement (evothyroxine/Synthroid).

Other endocrine glands are also subject to auto-immune inflammation in this setting. Inflammation of the pituitary gland, also known as hypophysitis, can lead to vision changes, confusion, headaches, and other neurologic issues. Similarly, the adrenal glands may become inflamed, leading to nonspecific symptoms such as fatigue, nausea, and low blood pressure or blood sugar. Both of these complications are treated with steroid therapy to reduce inflammation, as well as replacement of deficient hormones.

The lungs are also subject to inflammation, or pneumonitis, in about 1% to 3% of patients. The common symptoms of pneumonitis include shortness of breath, cough, and wheezing and are often associated with low oxygen-saturation levels in the blood. Changes in the appearance of
the lungs are visible on a CT scan, but diagnosis is definitively made with a biopsy, commonly done at bronchoscopy. Along with supplemental oxygen, possibly antibiotics, other supportive measures, or steroids are the cornerstone of treatment.

Rash is another very common side effect of immunotherapies, often appearing as a red, bumpy, and potentially itchy rash on the trunk, hands, and feet, although it may also be more diffuse. At its most extreme, the rash may cause severe blistering that may be very serious and require hospitalization, although, fortunately, a rash this severe is very rare. Mouth sores/ulcers may also be seen. Management is based on the severity of the rash and may require as little as topical steroids and medications for itching to IV steroids.

Other organs, including the liver, kidneys, and brain/nervous system, may also develop immune-mediated inflammation. Accordingly, clinical trials and increasingly common use of these immunotherapies in routine practice will always require vigilant follow-up with the cancer care team, including regular physical examinations and blood work, as well as close communication about new symptoms between scheduled visits. Most side effects are able to be treated effectively and are reversible if detected and addressed readily.

Summary

Immuno-oncology has evolved dramatically over the past few years from an approach with limited applicability, often accompanied by skepticism about its broad utility, to a strategy with clear evidence of efficacy that is poised to transform our management of many cancer types, potentially from early-stage to metastatic disease. Trials with multiple agents are ongoing, leading to expected new approvals in the next few years. Nevertheless, our enthusiasm about the benefits of these treatments must be tempered by a recognition that the dramatic and prolonged responses seen in some patients with melanoma, lung cancer, renal cell carcinoma, bladder cancer, and several other cancer types are not demonstrated by the vast majority, but rather by a limited subset. We also do not yet have a reliable biomarker or clinical profile to identify prospectively which patients are likely to be the major beneficiaries. While immunotherapies are typically quite well tolerated, they have the potential for a complex array of side effects that may be severe, develop late in the treatment, and be challenging to manage.

Taken together, evidence suggests that we are on the cusp of incorporating immunotherapies as an integral component of treatment for many more cancer patients in the coming years, but we await the results of ongoing clinical research to better understand which patients will benefit and where and how to best assimilate them into care plans or substitute them for existing treatment strategies.

*This educational summary is intended for patients with cancer, their caregivers, and other interested non-clinicians, and is part of a broader educational platform focused on immuno-oncology, available at [www.peerviewpress.com/e158](http://www.peerviewpress.com/e158)*

*The Immunotherapy Primer for Patients is a collaboration between GRACE and PVI, PeerView Institute for Medical Education*