The Practical Oncologist

John Kirkwood, MD
Professor of Medicine and Dermatology
Vice Chairman for Clinical Research
Department of Medicine
University of Pittsburgh
Director, Melanoma and Skin Cancer Program
University of Pittsburgh Cancer institute
Pittsburgh, Pennsylvania

Why is there a risk evaluation and mitigation strategies (REMS) requirement for ipilimumab?

Hello, my name is Dr. John Kirkwood and I currently serve as the director of the Melanoma Center at the University of Pittsburgh as well as a consulting attending physician at the Pittsburgh VA Medical Center.

I am frequently asked by clinicians who provide health care for melanoma patients why is there a risk evaluation and mitigation strategies (REMS) requirement for ipilimumab? This is a good question. As a reminder, REMS is a strategy to manage a known or potential serious risk associated with a drug or biological product. Bristol-Meyers Squibb has informed health care professionals about the risk evaluation and mitigation strategy, developed in collaboration with the FDA, which is required to ensure that the benefits of ipilimumab outweigh the risks of severe and fatal immune-mediated adverse reactions.

The ipilimumab REMS consists of a communication plan to inform health care professionals of the serious risks of ipilimumab, to facilitate early identification of these risks, and an overview of recommended management of patients with moderate or more severe immune-mediated adverse reactions. Ipilimumab was approved in March 2011 with the prescribing information including a boxed warning stating that use of the product can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions observed in clinical trial were enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.

Health care providers have been advised to read the boxed warning and accompanying full prescribing information for a complete description of these risks and their management, as well as to discuss the risks that may be associated with therapy with patients and their caregivers. Clinicians have been specifically instructed to permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid

therapy for indentified severe immune-mediated reactions. They have also been instructed to assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy, and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose.

Finally, health care professionals and patients are encouraged to report adverse events, side effects, or product quality problems related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program. A link to the approved REMS Communication Plan can be found at: www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM249 435.pdf

Nurses play an important part of patient health care regarding the education and monitoring of patients for side effects. Recognizing this role, the communication plan materials specifically include the "*Nursing Immune-mediated Adverse Reaction Checklist*" which includes a checklist with key questions to ask patients and actions to take when assessing patients for ipilimumab immune-mediated adverse reactions.