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CME Review

Desensitization to protein kinase inhibitors
A systematic review

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INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review article in this issue and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
- Read the article and reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned. At this time, physicians will have earned up to 1.0 *AMA PRA Category 1 Credit™*. Minimum passing score on the post-test is 70%.
- Approximately 4-6 weeks later you will receive an online outcomes assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive MOC Part II credit from the American Board of Allergy and Immunology.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the role of skin testing in protein kinase inhibitor desensitization protocols
- Apply principles of evidence-based practice to develop an appropriate patient-specific desensitization treatment plan and select optimal supportive care medications for patients undergoing desensitization

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Expiration Date: June 30, 2019

Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

Accreditation

The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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All identified conflicts of interest have been resolved.

Disclosure of Relevant Financial Relationships

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Introduction

Cancer is responsible for more than half a million American deaths every year and an estimated 39% of men and women will be diagnosed with at least 1 type of cancer during their lifetime.[1] Cytotoxic agents were previously the mainstay of therapy and continue to be used frequently in oncology practice, but their nonspecific mechanism of action is associated with extensive adverse effect profiles. The development of "targeted" therapies in the form of biologic agents and protein kinase inhibitors (PKIs) revolutionized cancer treatment and dominate the oncology drug pipeline. PKIs are small-molecule kinase inhibitors that act on various receptor targets by inhibiting signal transduction and preventing downstream effects that, uninhibited, promote cell growth and proliferation. Adverse effects still occur with PKIs, but they are often well tolerated and associated with improved quality of life.[2,3] In addition, PKIs offer the opportunity for oral regimens, instead of infusions, and in some circumstances might be more effective at prolonging progression-free and overall survival than traditional antineoplastic agents.[2–5] A diverse group, PKIs are used in a multitude of different cancers, often in the metastatic setting. Unfortunately, most cancers still have a limited number of effective treatment options and patients often will progress through all lines of appropriate therapy. In these disease states, in which the number of available pharmacotherapy options is limited and the mortality rate without intervention is high, allergic drug hypersensitivity is a potential barrier to treatment.

Adverse drug reactions are classified as type A or B. Type B reactions are dose independent and unpredictable; they are estimated to account for 10% to 15% of reported adverse drug reactions.[6] Drug hypersensitivity reactions are considered type B in nature, but the exact incidence is not known. Epidemiologic data have suggested that total drug hypersensitivity reactions can affect up to 20% of hospitalized patients and 7% of outpatients.[6] Immediate hypersensitivity reactions occur less than 1 hour after exposure and can be mediated by immunoglobulin E.[7] Reactions mediated by immunoglobulin E typically present as urticarial rash, pruritus, and angioedema.[8] Delayed hypersensitivity reactions do not appear until hours to days after the first exposure but can recur sooner with rechallenge.[7] The mechanism behind delayed reactions is not as well understood. Drug labeling will often list hypersensitivity as a contraindication for use.[9–12] Supportive care or dose lowering can be attempted to minimize the effects of the reaction, but the offending agent should be discontinued if the reaction cannot be controlled or avoided.

Desensitization is the measured reintroduction of small amounts of drug that are gradually increased to a full therapeutic dose, which could allow for improved tolerance and continued treatment.[8] However, providers are often hesitant to rechallenge a patient who has developed a drug hypersensitivity reaction and there is no universally accepted method for managing these reactions to PKIs. Often a singular PKI might represent the best treatment option for a patient. If alternative PKIs are available, they might not be appropriate because of interactions with medications, patient comorbidities, or financial burden. In addition, cross-reactivity between the various PKIs is not established, even for those with the same molecular targets or structural similarities. Theoretical potential exists for patients to develop a reaction or have cross-reactivity to specific functional groups within the PKI structure, such as sulfonamide groups. Confirming allergic hypersensitivity reactions also presents a challenge. Skin tests can be performed, but their diagnostic value has not been fully established for most drugs and their negative predictive value is generally low.[13] Positive skin test reactions might increase concern for reactions during desensitization and influence the number of premedications, administration setting, and duration of observation.