

Hypersensitivity Reactions to Oxaliplatin and Other Antineoplastic Agents

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Current Allergy and Asthma Reports 2008, **8**:56–62
Current Medicine Group LLC ISSN 1529-7322
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Although the reported incidence of hypersensitivity reactions (HSR) to antineoplastic agents is considered to be uncommon, it is difficult to evaluate their exact prevalence, mainly because their definition is vast and pathogenic mechanisms are vague. HSR include facial flushing, erythema, pruritus, fever, tachycardia, dyspnea, tongue swelling, rash/hives, headache, chills, weakness, vomiting, burning sensations, dizziness, and edema. Treatment and prevention consists of slowing the infusion rate, steroids, and type 1 and 2 histamine receptor antagonists. Desensitization could allow the small number of patients who experience severe HSR to receive effective therapy for their cancer. Reintroductions have only been reported as single case studies or small cohorts. Large-scale validation on desensitization strategies is still missing. With regard to oxaliplatin, knowledge of its rare but eminent toxicity is paramount, because this drug is widely used in treating colorectal cancer, the second-highest cause of cancer mortality in the United States.

Introduction

The use of most cytotoxic agents is associated with potential hypersensitivity reactions (HSR). *Hypersensitivity* is defined as an unexpected reaction that cannot be explained by the known toxicity profile of the chemotherapeutic agent [1]. HSR are seen with the use of several antineoplastic agents, including the taxanes (paclitaxel, docetaxel), asparaginase, the epipodophyllotoxins, procarbazine, doxorubicin, 6-mercaptopurine, and the monoclonal antibodies (cetuximab, trastuzumab, rituximab, and bevacizumab) [1]. Acute onset and delayed reactions have been described, which can cause flushing,

pruritus, urticarial rash, erythema, hypotension, dyspnea, bronchospasm, nausea, back pain, and drug fever [2].

Although HSR are considered to be uncommon, their exact prevalence is difficult to evaluate, because their definition is vast and the pathogenic mechanisms are vague. They are usually mild, ranging from itching and flushing to anaphylaxis, and they are reported only occasionally, as case reports. Although hypersensitivity reactions with respiratory arrest, cardiac collapse, and even death are rare, the incidence of mild-to-moderate reactions is underestimated in the oncology community, mainly due to the poor understanding of their pathogenesis: because many are reported as flushing, pruritus, heart rate, and blood pressure changes, an immediate-type hypersensitivity mechanism is suggested. On the other hand, nonimmunologic mechanisms have also been advocated, because many of these drugs may elicit mast cell mediator release directly. Therefore, not surprisingly, an inconsistency exists in terminology, grading, and management of these events, often resulting in the discontinuation of a potentially beneficial treatment [1,3].

The group of platinum-containing agents (cisplatin, carboplatin, oxaliplatin) is considered high risk for the development of HSR. Oxaliplatin (C₈H₁₄N₂O₄) (Eloxatin; Sanofi-Aventis, Bridgewater, NJ) is a third-generation organoplatinum compound, in which the platinum atom is complexed with diaminocyclohexane and an oxalate ligand. It is approved for the second-line (in 2002) and first-line (in 2004) treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU) and leucovorin (LV) [4], and for the adjuvant treatment of stage III colorectal cancer (in 2006) [5]. In addition to colorectal cancers, oxaliplatin is active in other malignancies, including pancreatic and gastric cancers. Its administration is very convenient for patients and oncology departments because it is safely administered in the outpatient setting. Oxaliplatin is now widely used in various combinations with 5-FU/LV and capecitabine-based regimens, as well as with bevacizumab, an antineovascular monoclonal antibody that binds to vascular endothelial growth factor [4,5].

The taxanes (paclitaxel and the semisynthetic docetaxel) are used as frontline treatment of non-small cell lung, breast, and ovarian cancers, and they have

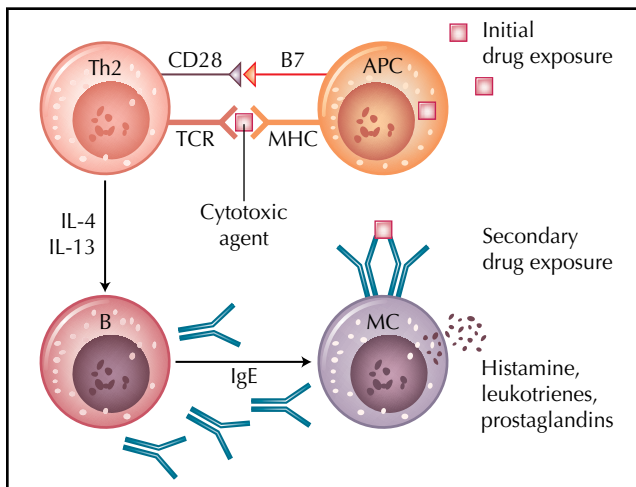


Figure 1. Type 1 immunoglobulin (Ig) E-mediated allergic reaction. APC—antigen presenter cells; B—B-leukocytes; MC—mast cells; MHC—major histocompatibility complex; TCR—T cell receptor; Th—T helper.

some role in other malignancies. Although HSR to taxanes occur more frequently in patients with atopy history, there is no evidence of specific immunoglobulin (Ig) E involvement. With regard to paclitaxel, there is some evidence that reactions may also result from sensitivity to the excipient, Cremophor EL (BASF Corporation, Florham Park, NJ), a polyoxyethylated castor oil added to solubilize the drug (527 mg in each mL of paclitaxel solution). Cremophor EL is thought to induce needle-like structures and micelles that induce complement activation and are suspected as a cause of anaphylactic-like reactions [1–3].

The epipodophyllotoxins (teniposide and etoposide) are used to treat neurologic, testicular, lung (small cell), and hematologic malignancies. Although they share the same molecular structure (teniposide differs from etoposide by the substitution of a thenylidene group on the glucopyranoside ring), no data suggest cross-sensitization. Finally, the excipients of etoposide (polysorbate 80) and teniposide (Cremophor EL, 500 mg/mL of drug solution) are suspected to induce some HSR [1,2].

L-asparaginase is an enzyme derived from *Escherichia coli* or from the parasitic bacteria *Erwinia*, and it is used to treat acute lymphoblastic leukemia. The reaction rate with intravenous administration is very high (6%–45%), whereas the intramuscular or subcutaneous routes are associated with a lower reaction rate. Reactions are more frequent in high doses, when the patient receives it daily and when the drug is given alone [1–3].

Classification and Pathogenesis of Drug-induced Allergic Reactions

Most drug-induced reactions (80%), including toxicity, side effects, and drug interactions, are predictable and related to the pharmacologic action of the drug.

The minority of drug reactions (approximately 20%) is unpredictable and usually not related to the pharmacologic actions of the drug. The majority of these are immune-mediated (so-called allergic or hypersensitivity reactions [HSR]), comprising 6% to 10% of adverse drug reactions. The remaining 10% are idiosyncratic reactions (aberrant reactions, not explicable by the pharmacology of the drug) or drug intolerance reactions (unwanted drug effect produced at subtherapeutic dosages), and their incidence relies on genetic and environmental factors [2].

The pathophysiology of HSR to cytotoxic agents is not well understood, but several mechanisms have been suspected. Development of such reactions usually occurs after multiple infusions, suggesting the need for sensitization to occur, and are described as type 1 allergic reactions resulting from the degranulation of mast cells and basophils following IgE binding to these cells. Histamine and other cytokines (leukotrienes, prostaglandins) with strong inflammatory potential are released, leading to the contraction of smooth muscles, dilation of capillaries, and subsequent development of the clinical signs described previously. Early symptom onset during oxaliplatin and paclitaxel administration provides further support to the above explanation [6] (Fig. 1). Type 2 complement-mediated, killer cell-activated reactions with thrombocytopenia, hemolysis, and Evan's syndrome and type 3 delayed vasculitic urticaria have also been described following platinum compounds administration [6–9].

Idiosyncratic reactions to the drug are not antibody related, and their onset is usually delayed instead of immediate. Santini et al. [10] reported a case of such an idiosyncratic reaction, occurring several hours after the completion of oxaliplatin infusion; the serum analysis of the patient showed elevated tumor necrosis factor- α and interleukin-6. The investigator postulated it to be a T-cell-mediated reaction [10]. It was also postulated that oxaliplatin acted as a superantigen on mononuclear cells and resulted in the release of these cytokines.

Other suggested mechanisms include binding of the platinum salts to different peptides of the major histocompatibility complex. In fact, HLA phenotype is a significant determinant of occupational sensitization to inhaled hapten of complex platinum salts, and the strength of this association varies according to the intensity of exposure [11,12]. Furthermore, the relationship between hypersensitivity reactions and HLA haplotype has been described for other drugs. Additional factors are deemed necessary to the immune system for developing the reaction after several infusions [13].

Platinum compounds can commonly induce HSR after an exposure period that usually requires several courses of administration. This suggests a truly immunologic reaction, although additional mechanisms cannot be ruled out.

Table 1. Characteristics of hypersensitivity reactions with different platinum compounds

	Cisplatin	Carboplatin	Oxaliplatin
Incidence	5%–20% (increased with radiation)	16%	12% (14), < 1 % grade 3–4
Initial onset	Data not available	After 6 cycles (range 2–12)	After 7 cycles (range 2–25)
Time of onset	Minutes	Minutes–days	Minutes–hours
Symptoms	Variable (fever, anxiety, pruritus, cough, dyspnea, diaphoresis, angioedema, vomiting, bronchospasm, rash and pruritis, and hypotension)	Variable (itching rash, chest tightness, blood pressure changes, facial swelling)	Variable (flushing, alterations in heart rate, dyspnea, back pain, fever, pruritis, erythema, nausea, rash)
Can it be reintroduced?	Data not available	Yes, with slowing the infusion rate (6% discontinued)	Yes, with premedications, slowing the infusion rate, and/or desensitization

Incidence

HSR following oxaliplatin exposure may occur within minutes of its administration and with any cycle of therapy. Nevertheless, the incidence increases with multiple courses of therapy [2,7], indicating that prolonged exposure to the agent has a role in a patient's sensitization. This is consistent with type 1 HSR, which are associated with repeated exposure to the agent. It has been reported to occur in a minority of patients (2% to 12%) who receive oxaliplatin, and less than 0.50% of them develop grade 3 or 4 reactions [7,14–16]. However, the incidence of HSR from oxaliplatin is on the rise recently as a result of its increasing clinical use both in the adjuvant and metastatic treatments of colorectal cancer. This trend is expected to continue in the near future [17,18]. Siu et al. [17] recently reported the epidemiologic and clinical features of oxaliplatin-related HSR. Among 180 patients, 15% were labeled as allergic to oxaliplatin, the proportion being higher among those receiving oxaliplatin in palliative second-line settings (19.6%) than in adjuvant or palliative first-line settings (10.2%). Overall, 2.2% of them developed grade 3 or 4 reactions. Re-exposure to oxaliplatin in 14 patients resulted in 28.6% HSR with 14.3% reactions of grade 3 or 4 intensity. The symptoms are usually mild, but because life-threatening anaphylactic reactions may occur, the US Food and Drug Administration (FDA) and Sanofi-Aventis have included a black-box warning for such reactions [19]. The differences in the reactions developed by oxaliplatin compared with the other platinum compounds are summarized in Table 1.

With regard to taxanes, all patients receive pretreatment with steroids and antihistamines before each dose, which usually includes 40 mg of dexamethasone or equivalent orally 12 and 6 hours before administration plus diphenhydramine and a histamine type 2 (H_2) receptor antagonist 30 minutes before the infusion. With this pretreatment, the reaction rate decreases to 1% to 2% compared with 2% to 5% without pretreatment [1].

Because both epipodophyllotoxins induce hypotension in 1% to 2% of patients following rapid intravenous

infusion, the drugs should be infused slowly over a period of 30 to 60 minutes. Teniposide is associated with a higher frequency of HSR compared with etoposide (52% vs 34%) [1,2].

The reaction rate with intravenous administration of L-asparaginase is very high (up to 45%) with most reactions occurring within 1 to several hours after administration. For this reason, it is almost always given intramuscularly or subcutaneously, with lower incidence of HSR (14%). The mean time of reaction is 7 days (range 1–11 days). Retreatment is associated with an increased risk (24%), as expected [1,2].

Clinical Manifestations

The clinical features are variable and unpredictable. Allergic reaction symptoms include pruritus, urticaria, angioedema, palmar erythema, facial flushing, erythematous rash, dizziness, diarrhea, nausea, back pain, chest discomfort, drug fever, facial or lingual swelling, tachycardia, and hypotension or hypertension [17,18]. More severe reactions may include chest pain, angina pectoris, bronchospasm, anaphylaxis, respiratory arrest, and even death. Idiosyncratic reactions, consisting of chills, fever, abdominal pain, and diarrhea, occur several hours after initiation of infusion. In such reactions, bronchospasm, cutaneous signs, and severe hypotension are absent, which stands against an anaphylactic mechanism.

Management

Table 2 displays the most commonly used cytotoxic agents associated with HSR and their clinical indications. It is obvious that almost every patient treated for an antineoplastic disease has the potential for developing an HSR. Attempts to identify patients likely to develop HSR following administration of cytotoxic agents are more or less ineffective. Therefore, efforts have focused on managing HSR when they occur and attempting to continue antineoplastic treatment without further

Table 2. The most commonly used cytotoxic agents associated with hypersensitivity reactions and their indications

Agent	Indications
Cisplatin	NSCLC, SCLC, ovarian, H&N, testicular, esophageal
Carboplatin	NSCLC, SCLC, ovarian, breast, H&N, testicular
Eloxatin	Colorectal, pancreatic
Paclitaxel	NSCLC, breast, ovarian
Docetaxel	NSCLC, breast, prostate
Fluouracil	Colorectal, pancreatic, gastric, breast, H&N
Etoposide	SCLC, testicular, sarcomas
Teniposide	Hematologic malignancies
L-asparaginase	Acute lymphoblastic leukemia
Doxorubicin	Breast, sarcomas

H&N—head and neck cancer; NSCLC—non-small cell lung cancer; SCLC—small cell lung cancer.

complications. As long as HSR are unpredictable in occurrence and degree of severity (despite any preventive measures), oncology departments should be prepared with standing orders to allow immediate intervention by the oncology nurses and physicians [20,21].

Immediate measures

When a HSR occurs, the infusion of the responsible drug should be stopped immediately, and airway, breathing, and circulation must be assessed rapidly to ensure their maintenance. The patient must be placed in recumbent position, with the lower extremities in an elevated position; continuous hemodynamic monitoring is essential. General measures include administration of oxygen at 6 to 8 L/min and of normal saline intravenously for fluid replacement and venous access. If severe hypotension exists, rapid infusion of volume expanders (colloid-containing solutions) might be necessary.

Specific measures that depend on clinical examination of the patient include the administration of 0.01 mg/kg (maximum dose, 0.5 mg) aqueous epinephrine (1:1000) given intramuscularly in 5 to 15 minutes as needed; 50 mg or more diphenhydramine in divided doses orally or intravenously with a maximum daily dose of 400 mg; and 50 mg ranitidine diluted in 5% dextrose to a total volume of 20 mL and injected intravenously over 5 minutes [22••]. In case of bronchospasm resistant to epinephrine, 2.5 to 5 mg nebulized salbutamol should be administered and repeated as necessary. For hypotension refractory to volume replacement and epinephrine injections, 400 mg dopamine in 500 mL of 5% dextrose in water may be administered intravenously to maintain adequate blood pressure. In patients receiving β -blockers, 1 to 5 mg glucagon should be administered intravenously over 5 minutes [22••]. Aspiration precautions should be observed because glucagon may cause nausea and emesis. Finally, systemic glucocorticosteroid, such as 1 to 2 mg/kg methylprednisolone every 24 hours,

are usually not helpful acutely but might prevent prolonged reactions or relapses [22••].

Reinstating the drug

After the reaction dissipates completely, the infusion should not be continued, and the administration of other scheduled drugs must also be reevaluated by considering the patient's clinical status after the reaction, the risk of additional toxicity, and the clinical utility of the chemotherapy. In patients who experience a mild HSR from a cytotoxic agent, a rechallenge may be attempted by reducing the infusion rate. It has been reported that prolonged administration of oxaliplatin (6 hours or more instead of the standard 2 hours) may prevent mild HSR and allow an uneventful continuation of treatment. Prolonged administration of both epipodophyllotoxins (over a period of 30 to 60 minutes) prevents drug-induced hypotension. Mild HSR to oxaliplatin and other platinum compounds can be improved in some patients with the use of steroids, antihistamines (diphenhydramine or loratadine), and H_2 antagonists (cimetidine, famotidine, or ranitidine) before administration of subsequent cycles [23••]. This is the standard procedure in taxane administration before each cycle; however, no data are available on the utility of pretreatment with steroids and antihistamines following L-asparaginase-triggered HSR.

Brandi *et al.* [14] evaluated application of the above strategies in a retrospective study of platinum salts. In a review of 124 patients, the authors reported fewer HSR when the infusion time was increased from the standard 2 hours to 6 hours. In this review, 17 of the 124 (13.7%) patients developed hypersensitivity. Of these 17, only two developed reactions at the end of the infusion; the rest exhibited reactions 10 to 15 minutes from the start of the infusion. Six of the 17 patients were successfully re-exposed after premedication with steroids and antihistaminic drugs. Five patients developed hypersensitivity symptoms again, and only one had no further reactions [7,24].

Patients who experience HSR should be monitored closely during and immediately after all successive infusions and should be strongly encouraged to report any discomfort they notice. Vital signs should be checked before, during, and after the infusion, although the possibility of a delayed reaction occurring hours after completion of the infusion cannot be ruled out. However, premedications cannot prevent all HSR, and mild reactions may escalate to severe reactions even when steroids and antihistamines are administered prior to oxaliplatin infusion [25]. Finally, in all cases of severe hypersensitivity, treatment should be discontinued and the patient switched to an alternative agent when possible.

Enduring the antineoplastic treatment

Mild-to-moderate reactions to antineoplastic compounds generally do not require treatment discontinuation, because most patients can continue therapy or be rechallenged (using pretreatment with antihistamines and corticosteroids) after symptoms have resolved. In addition, because no cross-reactivity among members of the same group has been observed, patients who are sensitive to one would tolerate well another compound of the same category, in most cases. However, rechallenge with platinum compounds is generally less successful than with taxanes: approximately 50% of patients rechallenged with platinum compounds experience recurrent HSR despite premedication. Patients who experience HSR to paclitaxel may try docetaxel as an alternative treatment; the latter is well tolerated by most patients who have reactions to paclitaxel, with only a 2% incidence of anaphylactic reactions. Also, patients who developed HSR to L-asparaginase could continue their treatment switching to the polyethylene glycolated (PEG) form, pegaspargase, which is better tolerated, especially when given intramuscularly. In fact, pegaspargase is specifically indicated for treatment in patients who are sensitive to the native drug, because approximately 70% of the patients who developed HSR to L-asparaginase will tolerate the PEG form, when given intramuscularly, whereas the percentage decreases to 40% when the drug is given intravenously [1,23••,25,26].

In more severe reactions (grade 3 and 4), rechallenge should be avoided and the agent responsible should be replaced. In any case, this decision should be based on balancing the risk for a serious, life-threatening, recurrent HSR reaction against the potential clinical benefit of further treatment. In palliative treatment, switching to an alternative agent (if available) seems more appropriate, but in cases of curative treatment continuing a beneficial treatment should be the priority. In the later instance, the application of a desensitization protocol should be considered [1,23••,25,26].

Allergy Tests

Skin testing has been used in the past to identify patients at risk for developing HSR (IgE-mediated), with a negative test result having an extremely high (96%) negative

predictive value [27•]. *Skin prick tests* were performed in small groups of patients with only a drop of solution to the forearm, with either undiluted pure injectable form or with oxaliplatin diluted in various concentrations (0.1, 1, and 10 mg/mL)—10 mg/mL of histamine or 9% codeine phosphate, and 0.9% saline were used as positive and negative controls, respectively. Positive reactions were defined as 3-mm or larger wheals when compared with the negative controls at 20 minutes. In addition, the sites were examined at 6, 24, and 48 hours.

Intradermal tests are performed when the results of skin prick tests are ambivalent or to further confirm the results, as in wheals of 4 to 6 mm—0.05 mL of oxaliplatin diluted at various concentrations (0.001, 0.01, 0.1, and 1 mg/mL) is injected intradermally on the ventral surface of the arm. Negative controls were performed with saline. Intradermal tests were considered positive if a two-fold increase in the diameter of the initial wheal after 20 minutes was observed. The wheals were examined again at 6, 24, 48, and 72 hours. When prick tests are strongly positive, intradermal tests should never be performed.

Until recently, investigators were discouraged from performing *patch tests* for chemotherapeutic drug allergies because they were considered to be too toxic. Nevertheless, in a recent study, patch tests were applied on the backs of patients using Finn Chambers on Scanpor tape (Epitest, Tuusula, Finland), and were read 48 and 72 hours later in accordance with the European Society of Contact Dermatitis guidelines [27•]. All patients tested had negative patch tests.

Drug rechallenge should not be attempted for those with a markedly positive skin test. It has also been reported that a patient with a negative skin test reaction still developed severe hypersensitivity after rechallenge with oxaliplatin. On the other hand, negative skin tests may also be seen in patients who have already experienced hypersensitivity. Two of eight patients with prior hypersensitivity reactions to oxaliplatin were reported by Meyer et al. [15] to have negative skin tests with oxaliplatin, as did one of three patients described by Thomas et al. [7].

In conclusion, skin prick and intradermal tests seem to have a very high negative predictive value, ranging from 0.92 to 0.99 in various series, whereas patch tests are of limited value [28–30]. Negative results of prick and intradermal tests would identify patients suitable for attempting to continue the oxaliplatin treatment; therefore, a standardized protocol of skin testing should be in place for all patients following the first HSR episode. Nevertheless, a negative skin test does not preclude the possibility of an allergic reaction or even anaphylaxis to oxaliplatin [31].

Desensitization Protocols

Desensitization protocols modifying the infusion rate have been implemented to reduce the risk of a second reaction following HSR. With regard to oxaliplatin, Mis et al. [31]

reported a 53-year-old woman with metastatic colon cancer who was treated with CAPOX (1000 mg/m²/day of capecitabine from Monday to Friday with 2 weekly doses of 85 mg/m² oxaliplatin) and 10 mg/kg bevacizumab. During the fifth cycle, she developed diaphoresis, hypotension, hypoxia, nausea, and abdominal cramps 12 minutes after the start of infusion. She was immediately resuscitated with fluid bolus, oxygen, diphenylhydramine (25 mg intravenously) and dexamethasone (10 mg intravenously). The fifth through seventh cycles were then without oxaliplatin. Because she had partial response to combination chemotherapy with oxaliplatin and she refused to take irinotecan (Camptosar; Pfizer, New York, NY) due to its toxicity profile, it was decided to desensitize her. On day 1 of desensitization, the patient was hospitalized and given prednisone 20 mg every 6 hours for a total of four doses. On day 2, 45 minutes before infusion, 8 mg of ondansetron and 20 mg of dexamethasone were administered. Then, 30 minutes before infusion, 50 mg of diphenhydramine and 300 mg of cimetidine were administered. Oxaliplatin was administered over 8 hours in serial dilutions from 1:10,000 to 1:1, and she received a total dose of 140 mg. Intravenous epinephrine (1:1000), diphenhydramine, and 125 mg of methylprednisolone were placed at bedside in case a reaction occurred. The patient tolerated the therapy without complications. The next infusion was given as an outpatient. Thus, desensitization helped this patient to receive an additional three doses. In this report, a 24-hour premedication schedule with serial dilution of oxaliplatin over a longer period of time was used based on reports for desensitization of carboplatin. Other investigators have developed similar desensitization protocols, varying in length of time, infusion rate, and pretreatment regimens [32,33].

Conclusions

The clinical benefits of novel chemotherapy agents such as oxaliplatin and the taxanes in the treatment of cancer are gaining momentum as more evidence emerges from the medical literature. Although the reported incidence of chemotherapy-induced HSR is low, the recent increasing incidence of HSR to these drugs anticipates an increase in their use in clinical practice [33,34]. Close monitoring, timely recognition, and effective management can prevent any serious, potentially fatal HSR. A few patients can be managed with premedication using steroids and antihistamines, but the majority of patients require either switching to another agent, or intensive desensitization. Due to the desensitization regimens, many patients might successfully continue to receive these agents, although large-scale validation of desensitization strategies is still missing. A careful balance of risk and benefit must be considered for the individual patient [35].

Disclosure

Dr. Saif has received honoraria for speaking for Sanofi-Aventis (Bridgewater, NJ), Genentech (San Francisco, CA), Bristol-Myers Squibb (Princeton, NJ), and Amgen (Thousand Oaks, CA). No other potential conflicts of interest relevant to this article were reported.

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