Infusion Reactions to Monoclonal Antibodies for Solid Tumors: Immunologic Mechanisms and Risk Factors

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The use of engineered monoclonal antibodies as antineoplastic therapy has been a significant advance within the past 15 years. These agents target various receptors and ligands required for the proliferation, survival, or maintenance of angiogenesis of tumors. Currently there are several agents approved by the US Food and Drug Administration for clinical use in solid tumors. Bevacizumab (Avastin) is a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF) and inhibits angiogenesis, and is currently approved for the treatment of colorectal, lung, and breast cancer (Avastin package insert, 2008). Trastuzumab (Herceptin) inhibits the HER2/neu receptor, and is utilized in both the adjuvant and palliative settings in breast cancer (Herceptin package insert, 2008). Two monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) are also in current use: the chimeric mouse-human antibody cetuximab (Erbitux), and the fully human antibody panitumumab (Vectibix) (Erbitux package insert, 2008; Vectibix package insert, 2008). These agents are both used in the treatment of colorectal cancer, and cetuximab has also been approved for the treatment of head and neck cancer.

Generally monoclonal antibodies are well tolerated and adverse events are specific to the target of the antibody, examples being skin rash with inhibitors of EGFR and cardiovascular toxicity with bevacizumab.[1,2] However, a subset of patients experience infusion reactions (IRs) following administration of the antibody therapy. Symptoms of IR range from mild (ie, chills, rash, etc) to severe, including severe anaphylaxis in rare incidences that are life-threatening.[3] As is widely known to oncologists, infusion reactions are not specific to the antibody-based therapy but also observed following administration of a variety of cytotoxic agents. For example, platinum agents such as oxaliplatin (Eloxatin) and carboplatin used in the treatment of colorectal and ovarian cancer respectively have been associated with IgE-mediated IRs.[4,5] For the purpose of a concise review, we will focus on the IRs associated with antibody-based therapies.

Clinical Risk Factors for Infusion Reactions

describing clinical risk factors that can accurately predict which patients will most likely experience IRs to antibody-based therapies. However, the risks of developing a fatal reaction due to general allergens such as foods, drugs, or insect stings have been evaluated.[6] The clinical risks that are pertinent to the cancer patient population and associated with severe reactions are a history of atopy, asthma affecting the airways, antihypertensive drugs, such as angiotensin-converting enzyme inhibitors or beta-blockers, and opioid drugs. These risk factors appear to be consistent with either comorbid conditions or pharmaceutical interventions that can worsen two major symptoms of the severe IRs: cardiovascular collapse and respiratory failure.

Similar clinical risk factors were examined in patients who developed the cetuximab-induced IRs.[7] Higher incidences of severe infusion reactions were observed following administration of cetuximab in comparison to other monoclonal antibodies used in the treatment of solid tumors.[8] When 143 patients treated with cetuximab were examined for the association between IRs and clinical risk factors including demographics, primary sites of cancer, and atopic history, only atopic history was significantly associated with the severe IRs. Patients with a history of atopy experienced more than
twice the rate of severe IR.[7] The atopic history included prior allergy to drugs, foods, and bee stings, as well as comorbid conditions with asthma, allergic rhinitis, or eczema.

Furthermore, it has been demonstrated that there is a markedly increased incidence of severe IRs among patients living in the middle portion of the southeastern United States.[7] In early studies of cetuximab, rates of severe IRs among patients in trials conducted in different regions of the United States and in the European Union were relatively low and consistent from region to region. Rates of severe IRs among these trials varied from no reported incidences to 3%. However, anecdotal observations made in treatment centers in the southeast region of the United States described a much higher incidence of severe infusion reactions to cetuximab. These observations were confirmed following analysis of patients treated with cetuximab in clinical trials in Tennessee and North Carolina, where the rate of severe (grade 3 or 4) IRs was 22%.[7] This unusual pattern of reactivity led to further study of a potential mechanism, as described below.

**Immunologic Mechanisms of Infusion Reactions**

The mechanisms by which monoclonal antibodies lead to IRs are in most cases not well characterized. Immunologic mechanisms associated with infusion reactions can be broadly classified as non-IgE mediated and IgE-mediated reactions. Although the mechanisms leading to infusion reactions vary, the clinical manifestations associated with IRs are often indistinguishable. The common symptoms include hypotension, dyspnea, rash, and tachycardia (Avastin package insert, 2008; Herceptin package insert, 2008; Erbitux package insert, 2008). There are also variations in the rates and timing of both mild and severe IRs to the monoclonal antibodies used in the treatment of solid tumors, suggesting that different therapies may induce different immunologic mechanisms resulting in the clinical manifestations of IRs.

A syndrome associated with IRs to monoclonal antibodies caused by non-IgE mediated mechanism is cytokine-release syndrome.[9] Monoclonal antibodies can bind to target cells, as well as other effector cells, such as mast cells. Binding of the antibody to the cell can initiate destruction of the cell, leading to the release of cytokines from both the tumor and effector cells. Cytokines released via this mechanism can lead to symptoms associated with infusion reactions. A definitive link for the monoclonal antibodies used in the treatment of solid tumors and cytokine-release syndrome has yet to be demonstrated, but this phenomenon has been observed in chronic lymphocytic leukemia patients treated with rituximab (Rituxan).[10]

A recently published case report demonstrated tumor lysis syndrome in a colon cancer patient 18 hours after receiving the first infusion of cetuximab monotherapy.[11] The mechanistic differences in the clinical manifestations between the tumor lysis syndrome and the IRs around the time of the first infusion should be recognized for appropriate management.

IgE-mediated IRs are type I allergic reactions that are characterized by release of cytokines from mast cells or basophilis. IgE-mediated reactions generally occur after an initial exposure to an antigen or allergen. Following internalization of an allergen, antigen-presenting cells, such as dendritic cells and B cells, present the processed peptides from the allergen to the T-helper cells as a peptide major histocompatibility complex. Upon binding to the complex with T-cell receptors, the T-helper cells are activated and release IL-4, IL-13, and CD154. CD154 is a ligand for CD 40, one of the receptors on the B cells, and induces isotype class switching to generate IgE in the activated B cells. Subsequently the B cells secrete allergen-specific IgE antibodies, which bind to mast cells or basophilis.[12] Upon a secondary exposure, the mast cells will bind to the allergen via the IgE antibody and stimulate release of the histamines, leukotrienes, and cytokines, which will induce an allergic response.

There have been conflicting reports about the nature of hypersensitivity reactions to infusion of monoclonal antibodies and whether they induce true IgE-mediated reactions, because the presence of antidrug-specific immunoglobulins requires a previous exposure to the drug.[3,8] A study in patients with Crohn’s disease treated with infliximab (Remicade), a chimeric mouse-human monoclonal antibody targeting tumor necrosis factor-α (TNF-α), demonstrated that the presence of anti-infliximab IgG antibodies in the serum was associated with an increased incidence of IRs and decreased efficacy.[13] Furthermore, the concentration of anti-infliximab antibodies and the incidence of IRs increased following multiple rounds of infusions, although there was no infusion reaction with the first dose.[13] This suggests that patients subsequently developed anti-infliximab antibody after being exposed by the first infusion. The timing of infliximab-related IRs is similar to that observed with the platinum agents, where IRs are observed after multiple rounds of therapy.[4,5] This contrasts to observations with cetuximab and other monoclonal antibodies used in the treatment of solid tumors, where most IRs occur during the first infusion. These observations suggest that different immunologic mechanisms are predominantly responsible for the IRs.
A recent report clarified this issue in the case of cetuximab by demonstrating that a majority of patients experiencing severe hypersensitivity reactions to cetuximab had detectable levels of IgE against the fragment antigen binding (Fab) portion of cetuximab in pretreatment sera.[14] The fact that the IgE was present in patients with no previous exposure to cetuximab suggested the presence of preexisting IgE that cross-reacts with cetuximab. Further study showed that the cetuximab cross-reacting IgE binds to a specific sugar moiety, galactose-α-1,3-galactose oligosaccharide, present on the Fab portion of cetuximab (Figure 1).[14] In fact, the culprit behind the creation of the specific carbohydrate moiety is actually the cell line in which cetuximab is produced; an SP2/0 mouse myeloma cell line, rather than the traditional Chinese hamster ovary cell used for production of many therapeutic monoclonal antibodies.[14] Interestingly, the incidence of the cetuximab cross-reacting IgE varies across the United States.[14] Sera obtained from control (noncancer) patients from the southeast region of the United States demonstrated a significantly higher presence of anticetuximab antibodies compared with other regions of the country that were tested, seemingly explaining the high IR rate that had been described for the region.[14] Unfortunately, the underlying cause of the regionality of this apparent antigenic “mimic” of cetuximab remains a mystery. Reasonable hypotheses given the distribution include parasitic infection or insect exposure that is present or native to the Southeast region.

Regardless of mechanism, the elucidation of anti-cetuximab IgE will allow for a simple and accurate test for patients in high-incidence areas that will allow clinicians to identify prospectively patients who would have severe reactions, so that the alternative therapy could be used preferentially. Furthermore, in a recent study, high levels of serum platelet-activating factor (PAF; one of the proinfl ammatory phospholipid secreted by mast cells, monocytes, and macrophages) were correlated with severe anaphylaxis, while PAF acetylhydrolase (PAF inactivating enzyme) activity was inversely correlated, suggesting low PAF acetylhydrolase activity resulted in decreased inactivation of PAF and in development of severe anaphylaxis (Figure 2).
2).[15] The measurements of the serum PAF levels and PAF acetylhydrolase activity may benefit patients who have clinical risk factors of severe IRs given antibody-based therapy as well as cytotoxic agents known to cause anaphylaxis.

Conclusions
Development of predictive assays, such as detection of cetuximab crossreacting IgE or high serum PAF levels and low PAF acetylhydrolase activity in the pretreatment sera, can alleviate the burden of managing severe anaphylactic reactions in the clinic. However, it is important to realize that infusion reactions can be both non-IgE-mediated and IgE-mediated reactions and they are difficult to discriminate based on clinical presentation. Therefore, clinics should be appropriately equipped to treat severe IRs, and staffs should be educated about the mechanisms of reactions and guidelines to properly manage the reactions.

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