Nondermatologic Adverse Events Associated With Anti-EGFR Therapy

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Dermatologic events are considered the most relevant elements of the toxicity profile of epidermal growth factor receptor (EGFR) inhibitors. However, some nondermatologic adverse events can also be common. Although these toxicities are rarely severe, they may have fatal outcomes if not managed appropriately. For example, gefitinib (Iressa) and erlotinib (Tarceva) (and more rarely, cetuximab [Erbitux]) are associated with a risk of interstitial lung disease, while the administration of cetuximab may be associated with infusion reactions. Preparedness to assess patients at risk and to manage symptoms promptly and effectively can greatly reduce any potential risks. As a result, anti-EGFR therapies are generally well tolerated. As anti-EGFR agents are integrated into standard regimens or combined with novel treatments, familiarity with their safety profiles will become increasingly important. This article reviews the key nondermatologic adverse events associated with cetuximab, gefitinib, and erlotinib, and summarizes the most important management recommendations.

The dermatologic effects of drugs that inhibit epidermal growth factor receptor (EGFR) signaling have received much attention, primarily because they affect nearly all treated patients and are the most visible adverse events,[1,2] and because they may be a marker of antitumor activity.[3,4] These effects, however, are not life-threatening, are manageable, and typically resolve after treatment. However, some nondermatologic adverse events associated with anti-EGFR therapy can also be characteristic, if not as common as skin manifestations. These toxicities are rarely severe, but they may have fatal outcomes if not managed appropriately.

Although some adverse events are common to all anti-EGFR therapy, some important differences have emerged among various classes of anti-EGFR agents as a result of different mechanisms of action and routes of administration (Table 1). For example, the monoclonal antibody cetuximab (Erbitux) is associated with infusion reactions that have not been observed with the orally administered tyrosine kinase inhibitors gefitinib (Iressa) and erlotinib (Tarceva). Gefitinib and erlotinib are associated with a risk of interstitial lung disease (ILD), which has rarely been reported with cetuximab. This article reviews key nondermatologic adverse events associated with cetuximab, gefitinib, and erlotinib.

Infusion Reactions
Incidence
Approximately 3% of patients treated with cetuximab experience a severe (grade 3/4) infusion reaction but fewer than 1 in 1,000 cases are fatal.[5] Milder reactions (grade 1/2) have been observed in 16% of patients treated with cetuximab plus irinotecan (Camptosar) and in 19% of patients treated with cetuximab alone.[6,7] The incidence of severe infusion reactions is similar to the incidence of hypersensitivity reactions seen with standard chemotherapy agents such as paclitaxel, 2% to 4%,[8,9] and oxaliplatin (Eloxatin), 2% to 3%.[10] Similar reactions have been observed with other therapeutic monoclonal antibodies that are widely used in clinical practice such as trastuzumab (Herceptin) and rituximab (Rituxan).[11,12]

Characteristics
Most reactions to cetuximab occur during the first infusion (90%), but some have occurred after multiple infusions.[5] Similar observations have been made with both trastuzumab and rituximab.[11,12]
Early signs of an infusion reaction often consist of changes in respiratory, cardiac, or integumentary status.[13] Typical respiratory effects include changes in the rate and depth of respiration, dyspnea, wheezing, stridor, and tightness of the chest. Signs of altered cardiac function include tachycardia, blood pressure changes, chest pain, rhythm changes, irregularities, distant or extra heart sounds, syncope, and dizziness. Changes in integumentary status may include localized or diffuse urticaria, diffuse erythema, pruritus, and angioedema of the face, eye area, earlobes, hands, and feet. Other signs of an infusion reaction include nasal congestion, rhinitis, sneezing, or tearing. Severe reactions are most often characterized by rapid onset of airway obstruction, including bronchospasm, stridor, hoarseness, urticaria, and hypotension.[14]

Management
Clinicians should be prepared for possible infusion reactions, particularly when a patient receives cetuximab for the first time. However, some patients have experienced their first severe reaction after multiple infusions; therefore caution is warranted during every infusion.[5] Standing orders should be in place in the event of an infusion reaction, and sufficient medical supplies (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, oxygen) and equipment should be on hand during all administrations in case a reaction occurs.[13,15] Standard premedication for cetuximab is intravenous diphenhydramine.

Because successful management of infusion reactions requires early recognition and prompt intervention, clinicians should be vigilant in monitoring patients receiving cetuximab. Vital signs should be checked and recorded just before the infusion, at regular intervals during the infusion (every 5 to 15 minutes), and after the infusion.[5,13] Monitoring the patient for 1 hour after the infusion is also recommended.[5] When given proper medical attention, most patients who experience an infusion reaction recover without consequences. Treatment algorithms for acute anaphylaxis, such as the one produced by the Joint Council of Allergy, Asthma and Immunology (JCAAI), may be followed (Figure 1).[16] At the first sign of a reaction, the cetuximab infusion should be stopped.[5,13] For mild to moderate reactions, treatment can continue using a reduced infusion rate once the symptoms have resolved.[5] For severe infusion reactions, cetuximab should be discontinued. In some cases, patients who had a severe infusion reaction may be successfully rechallenged with cetuximab.
Further research is needed to find ways to reliably identify patients who are at risk of infusion reactions during cetuximab treatment. Using a test dose before the first infusion has not been found to effectively identify at-risk patients.[5] Patients with a history of allergies or anaphylaxis should be evaluated thoroughly before receiving treatment. The JCAAI has produced an algorithm for the assessment of these patients.[16]

Interstitial Lung Disease

Incidence

Determining the incidence of anti-EGFR therapy-related ILD in non-small-cell lung cancer is complicated by many factors, including the underlying neoplastic disease, adverse events caused by
other chemotherapy agents, growth factor support, oxygen treatment, radiation therapy, and opportunistic infections.[17]

In a review of a safety information database on over 50,000 patients treated worldwide with gefitinib, 408 patients had ILD, 324 of whom were in Japan.[18] This resulted in a global incidence of about 1%, with a higher incidence in Japan (2%) and a lower incidence in the United States (0.3%). Smaller studies conducted in Asia have reported higher incidences, ranging from 4% to 6%. [19,20] Controlled clinical studies conducted in Western countries show that the incidence of ILD in patients treated with gefitinib or erlotinib is low and similar to that of patients treated with placebo.[21-24] These differences point to risk factors that are probably ethnicity-related.

To put the incidence of gefitinib-related ILD in perspective, it should be noted that severe lung disease occurs in 3% to 5% of patients treated with standard chemotherapy agents used routinely in the treatment of lung cancer,[17] including docetaxel (Taxotere),[25,26] paclitaxel,[8,27,28] gemcitabine (Gemzar),[29] irinotecan,[28,30,31] and vinorelbine.[28,32] “Chemotherapy lung,” acute ILD with pathologic features of diffuse alveolar damage, occurs in about 10% of patients treated with chemotherapy.[33] Notably, ILD has also been reported with imatinib (Gleevec), a tyrosine kinase inhibitor that does not target EGFR.[34]

Patients with existing pulmonary fibrosis or other pulmonary comorbidities may be at greater risk of developing ILD.[18,35,36] For these patients, careful attention should be given to clinical respiratory symptoms, especially during the first 1 to 2 months of treatment.[36,37]

Characteristics

The first signs of ILD are often dyspnea with or without cough or low-grade fever, which rapidly become worse and require hospitalization. Symptoms typically appear in the first 1 to 2 months of treatment; the median onset of ILD was 24 days in Japan and 42 days in the United States.[18] Characteristic CT chest findings include bilateral diffuse ground-glass opacities.[36,38]

Management

At the first signs of respiratory changes during treatment with gefitinib or erlotinib, treatment should be interrupted and a thorough investigation of pulmonary symptoms should be initiated. If ILD is confirmed, treatment should be discontinued.[18,39-41] Methylprednisolone can be used to treat respiratory symptoms,[42] and most symptoms resolve after anti-EGFR therapy has been discontinued.[37]

The presence and extent of parenchymal lung disease is best determined by high-resolution computed tomography (HRCT) and pulmonary function tests.[43] Definitive diagnosis of ILD requires a lung biopsy, which is not routinely performed in lung cancer patients. The use of clinical criteria and HRCT can rule out other possible diseases with a high degree of sensitivity (72% to 79%) and specificity (84% to 87%).[44] Other possible causes of pulmonary distress that should be excluded include infection, pulmonary embolism, cancer progression, radiation-related injury, fluid overload, and congestive heart failure.[37,39,42] In addition, clinicians should consider comorbid chronic obstructive pulmonary disease and aspiration of food and saliva, particularly in patients with vocal cord paralysis or brain metastases.[42]

Gefitinib-related ILD was found to be fatal in one-third of cases.[18] Therefore, clinicians should be aware of ILD and vigilant in monitoring respiratory symptoms in patients receiving gefitinib or erlotinib.[36] Death due to ILD can be prevented by promptly recognizing new-onset respiratory symptoms, discontinuing treatment, performing radiographic assessment, and starting glucocorticosteroid treatment when ILD is suspected.[37] Patients treated with gefitinib or erlotinib should be encouraged to seek immediate medical attention if they develop fever, cough, or dyspnea.[18]

Other Adverse Events

Cetuximab-Associated Hypomagnesemia

Hypomagnesemia has been reported in patients treated with cetuximab.[45,46] In a phase III study of cetuximab in patients with head and neck cancer conducted by the Eastern Cooperative Oncology Group, hypomagnesemia was reported in 8% of patients who received cetuximab, compared with 0% of patients in the placebo group.[47] Patients should be monitored for hypomagnesemia while receiving cetuximab, and magnesium repletion may be necessary in some patients.[5]

Other important toxicities seen with cetuximab monotherapy in patients with metastatic colorectal cancer include asthenia/malaise (all grades 48%), fever (27%), headache (26%), abdominal pain (26%), and pain (17%).[5]

Tyrosine Kinase Inhibitor-Related Diarrhea

Besides dermatologic toxicity, diarrhea is the most common adverse event associated with erlotinib and gefitinib; it is dose-limiting in some cases.[21-24,38,48,49] Two phase III studies of erlotinib...
reported grade ≥ 3 diarrhea in 6% of patients, compared with < 1% of patients receiving placebo.[23,48] For gefitinib, two phase III studies reported grade 3/4 diarrhea at 500 mg (12.0% and 25.4%) and 250 mg (3.6% and 9.9%) compared with placebo (2.3% and 2.9%).[21,22] In most cases, loperamide treatment controls erlotinib- and gefitinib-induced diarrhea.[38] Dose reductions and temporary treatment interruptions are recommended for erlotinib and gefitinib in patients who develop severe diarrhea.

Other Toxicities

Asymptomatic increases in liver transaminases have been observed with gefitinib and erlotinib.[38] Patients should be monitored regularly for changes in liver function (eg, transaminase, bilirubin, alkaline phosphatase), but intervention is not usually required.

Gefitinib was initially associated with ophthalmologic toxicity in several clinical trials, although it was never dose-limiting or cause for treatment discontinuation.[38] However, a review of patients treated with gefitinib in phase I and II trials revealed no evidence of any consistent drug-related ophthalmologic toxicity.[50] Gefitinib-related eye toxicity is typically an indirect result of excessive eyelash growth that causes corneal irritation or abrasion. Patients should be monitored during regular physical examinations and excessive eyelashes should be trimmed; if trichiasis occurs, patients should be referred to an ophthalmologist.[38]

Discussion

Anti-EGFR therapy is generally well tolerated. Besides skin rash, important adverse events associated with cetuximab include infusion reactions, which can be severe or fatal but rare and require preparedness for prompt and effective management. For most patients who experience an infusion reaction, cetuximab treatment should be discontinued. Other important adverse events associated with cetuximab treatment include hypomagnesemia, asthenia, and headache. One key nondermatologic adverse event associated with gefitinib and erlotinib is ILD, which is infrequently reported outside Japan but can be fatal if not recognized early. Treatment should be discontinued for patients in whom ILD is confirmed. Other important nondermatologic effects of gefitinib and erlotinib include diarrhea, which is generally manageable with loperamide but may require treatment delays or dose reductions. Further research is needed to develop ways to identify patients at risk for both infusion reactions and ILD.

Mutations in the EGFR gene that seem to determine sensitivity to tyrosine kinase inhibitors have recently been identified[51,52]; other studies have demonstrated that high gene-copy number (detected by fluorescence in situ hybridization) is associated with improved efficacy of tyrosine kinase inhibitor therapy.[53,54] Advances such as these, as well as others coming from proteomic studies, may help to select patients who are not only most likely to benefit from anti-EGFR therapy, but also may be less prone to experience serious side effects.[55]

The tolerability profiles of anti-EGFR therapy will become increasingly important as these agents are integrated into standard regimens and combined with other novel treatments. Preliminary experiences with gefitinib and erlotinib in combination with chemotherapy for metastatic colorectal cancer have resulted in excessive toxicity, including diarrhea and neutropenia, and early trial termination.[56,57] Whether excessive toxicity was due to pharmacokinetic/pharmacodynamic interactions with chemotherapy is unclear. The combination of cetuximab with cytotoxic agents, however, does not seem to exacerbate the toxicity of chemotherapy regimens and appears to be feasible, as demonstrated by favorable profiles observed in patients with metastatic colorectal cancer, non-small-cell lung cancer, or squamous cell carcinoma of the head and neck.[6,47,58]

Combining anti-EGFR therapies with agents that target vascular endothelial growth factor receptors such as bevacizumab (Avastin) is another promising approach.[59,60] The combination of erlotinib and bevacizumab produced encouraging antitumor activity and had an acceptable safety profile in a phase I/II trial in patients with non-small-cell lung cancer.[61] In a randomized phase II trial assessing cetuximab plus bevacizumab with or without irinotecan in patients with metastatic colorectal cancer, Saltz et al[62] reported that concomitant use of both monoclonal antibodies was feasible with no clear indication of increased toxicity.

These therapies also seem to provide safe options in combined modality regimens. Ongoing trials are investigating the feasibility and efficacy of anti-EGFR tyrosine kinase inhibitors in radiotherapy-based regimens. A large randomized trial has already demonstrated that the addition of cetuximab to standard radiotherapy regimens preserves quality of life and does not exacerbate the major toxicities typically associated with radiation in patients with head and neck cancer, including mucositis, dysphagia, or xerostomia.[63]

Further development of anti-EGFR therapies in these and other combinations and clinical settings will depend on careful assessment and management of drug-related adverse events.
Disclosures:
Dr. Sandler has served as a consultant for Bristol-Myers Squibb/ImClone, and OSI Pharmaceuticals, and has been a consultant and served on a Speakers Bureau for Genentech.

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