Management of Side Effects for Patients Receiving Multimodality Therapy in Thoracic Oncology

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Annual deaths from lung cancer exceed those from breast, prostate, and colon cancer combined. Since lung cancer is frequently life-threatening, many patients are constantly on treatment, according to information presented at JADPRO Live 2018 by Marianne Davies, DNP, RN, CNS, ACNP, AOCNP®, of the Yale University School of Nursing and Medicine and Yale Comprehensive Cancer Center, and Beth Eaby-Sandy, MSN, CRNP, of the Abramson Cancer Center, Hospital of the University of Pennsylvania. With continuous cancer therapy comes a host of side effects; therefore, learning to recognize and treat the adverse events caused by various multimodality therapies is crucial to caring for patients with thoracic malignancies.

"Lung cancer is common, but it is also very deadly," said Ms. Eaby-Sandy. "Because of that reason, our patients do not have treatment breaks frequently; they are on treatment for metastatic disease almost all of the time."

EGFR INHIBITOR TOXICITIES

In non–small cell lung cancer (NSCLC) patients treated with epidermal growth factor receptor (EGFR) inhibitors, rash is the most common toxicity. This acne-like rash can range from very mild to severe and tends to appear on the face and chest. Incidence varies significantly depending on the drug used (Table 1). (Cetuximab [Erbitux] and panitumumab [Vectibix] are not approved by the US Food and Drug Administration [FDA] for NSCLC, but are sometimes used.)

EGFR inhibitor–associated rash tends to be worse in areas that have received prior sun exposure, Ms. Eaby-Sandy noted. Patients might present with rash on the entire face, except for where sunglasses blocked the sun, or only in the "V" area, if they wore V-neck T-shirts frequently over many years.

The occurrence of rash does tend to be a significant predictor of clinical benefit from EGFR inhibitors, but this is not applicable to patients with an *EGFR* mutation who are taking osimertinib (Tagrisso; Liu

Table 1. Incidence and Severity of Rash

Agent	All rash incidence	Grade 3/4 rash incidence
Cetuximab	89%	12%
	(70% in FLEX trial)	(10% in FLEX trial)
Erlotinib	First line: 85%	First line: 14%
	Second line: 75%	Second line: 9%
Panitumumab	89%	12%
Gefitinib	First line: 66%	First line: 3%
Afatinib	First line EGFR: 90%	First line: 16%
	Squamous NSCLC: 70%	Squamous NSCLC: 7%
Osimertinib	41%	0.50%
Dacomitinib	78%	21%

Note. EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer. Information from Mok et al. (2009); Pirker et al. (2009).

et al., 2013). "Now, with osimertinib being available in the first-line setting, we have seen significantly less rash with this drug," Ms. Eaby-Sandy noted, adding that preemptive treatment is not recommended for these patients because the rash is minimal.

To prevent rash, she advises patients to use moisturizers with added sun protection factor and without dyes or fragrances, and to wear protective clothing. Erlotinib (Tarceva) or afatinib (Gilotrif) can be taken on an empty stomach to regulate absorption, as food speeds up absorption and causes more significant toxicities. Other drugs, such as gefitinib (Iressa), osimertinib, and dacomitinib (Vizimpro), can be taken with or without food. Patients should also avoid very hot showers, direct sunlight, and extreme temperatures.

Treatment recommendations from the Multinational Association of Supportive Care in Cancer (MASCC) include alclometasone 0.05% cream, fluocinonide 0.05% cream twice daily, and clindamycin 1% as topical treatments. Systemic options include doxycycline at 100 mg twice daily, minocycline at 100 mg daily, and isotretinoin at low doses, 20 to 30 mg/day (Lacouture et al., 2011).

Trichomegaly, the excessive growth and curling of eyelashes, can be significant, and is usually a longer-term side effect. "We recommend trimming eyelashes carefully, but if they are curling in, consult ophthalmology," she advised. "This can certainly develop into blepharitis, conjunctivitis, infections, and scratching of the cornea."

Paronychias, or inflammation around the nail beds, can occur on the fingers or toes. It is usually inflammatory and not bacterial, due to the inhibition of epidermal growth factor in these areas, but it is still important to culture for bacteria to guide systemic therapy. Diluted vinegar or bleach soaks, topical steroids, or even cauterization with silver nitrate may be used for inflammation. For difficult cases, consult a dermatologist or a podiatrist for consideration of a partial nail avulsion, so as to avoid holding the drug.

"Paronychia is a real thing that we still struggle with. While osimertinib doesn't cause as much rash, it causes paronychias just as much as, if not more than, other EGFR inhibitors," she said.

"It's worth sending patients with paronychias to the dermatologist. There is less medication adherence when patients have really painful side effects. If they can't get their shoes on and they can't walk, they might stop taking their drugs."

The speakers advised the use of thick moisturizing creams for fissuring and cracking of the skin. MASCC guidelines recommend using super glue to glue cracks and fissures together to avoid infection. Scalp rash can be difficult to manage, but selenium-based shampoos or fluocinonide solution/shampoos can help. Topical or oral antihistamines, as well as moisturizers, are recommended for pruritus, psoriasis, itching, and dry skin (Lacouture et al., 2011).

Diarrhea is the second most common side effect of EGFR inhibitors. Its incidence is 50% to 60% across EGFR inhibitors (other than dacomitinib or afatinib, which have a higher rate), but grade 3 to 4 diarrhea occurs in only about 2% of patients receiving osimertinib. Diarrhea from EGFR inhibitors should be managed with loperamide, diphenoxylate/atropine, hydration, and electrolyte repletion, or dose reductions (which are often necessary with afatinib).

EGFR INHIBITOR CONSIDERATIONS

Side effects and their incidence can vary from drug to drug. Of the available EGFR inhibitors,

dacomitinib was granted FDA approval most recently and has demonstrated superiority over gefitinib in the first-line setting (Mok et al., 2018). However, there is still no head-to-head comparison with osimertinib, which is now the most commonly used EGFR inhibitor. Osimertinib led to better progression-free survival in a head-to-head study vs. gefitinib/erlotinib, and appears to be the least toxic of the currently available EGFR inhibitors (Soria et al., 2018).

While the 40-mg dose of afatinib is approved, data from a post-hoc analysis showed that 30 mg was equivalent to 40 mg in terms of both pharmacokinetic features and progression-free survival (Yang et al., 2016), and the 30-mg dose is better tolerated.

TOXICITY MANAGEMENT OF ALK/ROS1 AND BRAF INHIBITORS

For patients with NSCLC on anaplastic lymphoma kinase (ALK) and ROS1 inhibitors, side effects will vary depending on the drug.

Crizotinib (Xalkori), the standard of care for many years, causes visual changes in about 70% of patients during the first 3 months of treatment. Patients struggle to adjust from dark to light, so driving at night is not recommended at the start of treatment.

Pneumonitis caused by crizotinib can be severe. "I want to clarify that pneumonitis from tyrosine kinase inhibitors (TKIs) is usually much worse," said Ms. Eaby-Sandy. "Whether it is an EGFR inhibitor, an ALK inhibitor, or an oral tyrosine kinase inhibitor (TKI), this is severe and requires a permanent discontinuation. We do not rechallenge with these drugs, other than brigatinib, which can be dose reduced and rechallenged after symptoms improve." Patients who present with acute onset shortness of breath should be sent for a computed topography (CT) scan right away, she advised.

Ceritinib (Zykadia) for *ALK*-positive NSCLC can lead to severe gastrointestinal (GI) toxicity in a large number of patients. However, recent data support a significantly lower dose: 450 mg daily with food instead of 750 mg, with less GI toxicity (Cho et al., 2017).

Alectinib (Alecensa) at 600 mg daily is generally used in the first-line setting due to its superiority over crizotinib, but it can raise creatine phosphokinase (CPK) levels. This can lead to significant myalgias in some patients, underscoring the need to check CPKs regularly. Follow institutional guidelines regarding dose reduction in these patients, Ms. Eaby-Sandy said.

Brigatinib (Alunbrig) is administered as a single pill, once a day. Pneumonitis rates are much higher with this drug when compared to others, although usually less severe, and patients on brigatinib can usually reduce their dose and be retreated. "That's why there is a run-in of 90 mg daily," she explained. "If the patient tolerates that, go up to 180 mg, but if they develop pneumonitis, then hold the drug and dose reduce."

Lorlatinib (Lorbrena), which was most recently approved for the treatment of patients with *ALK*-positive metastatic NSCLC who have progressed on one or more ALK TKIs, tends to have many of the same side effects as other ALK inhibitors (nausea, GI toxicity, and edema), in addition to hypercholesterolemia.

BRAF inhibitors, such as dabrafenib (Tafinlar) and trametinib (Mekinist), although used rarely in lung cancer, can produce high fever. For fevers of 102 to 104 degrees, or complicated fevers, the drug should be held, and the patient can usually be restarted at the same dose. "You don't always have to dose reduce for fever," she noted.

Other toxicities of targeted agents are shown in Table 2. Ms. Eaby-Sandy advised advanced practitioners to always study the package insert, and certainly to do so when new drugs are approved. "We should know when side effects are going to happen, and we can educate patients about them."

TOXICITIES OF IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors have become the mainstay of treatment for patients with lung cancer. They work by promoting T-cell activity, but that activation cannot be confined to antitumor effects alone, and can lead to unrestrained T-cell attack on any organ system. The first step in terms of managing patients on immune checkpoint inhibitors is to rule out any other cause for toxicities; if no other cause is identified, assume it is an immune-related adverse event (irAE), Dr. Davies advised.

Table 2. Toxicities of Targeted Agents

Toxicity	Agents	Considerations
Diarrhea	EGFRIs and ALKIs	Loperamide; diphenoxylate/atropine; hydration and electrolyte replacement; dose reduction
ILD/Pneumonitis	EGFRIs, ALKIs	CTA; consider discontinuation
Cardiotoxicity (cardiomyopathy, QT prolongation, bradycardia)	EGFRIs (osimertinib), ALKIs, BRAFIs	Echo; consider dose reduction
Hepatoxicities	EGFRIs, ALKIs	Monitor LFTs; consider dose reduction
Visual changes	ALKIs, BRAFIs	Recommend no driving at night
Edema	Crizotinib, alectinib	May need diuretics
Hyperglycemia	Ceritinib, BRAFIs	Monitor blood glucose levels regularly
Myalgias	ALKIs	Monitor CPK
Pyrexia/Fever	BRAFIs	Temperature > 104°, hold and dose reduce

Note. EGFRI = epidermal growth factor receptor inhibitor; ALKI = anaplastic lymphoma kinase inhibitor; ILD = interstitial lung disease; CTA = computed tomographic angiography; ECHO = echocardiogram; BRAFI = B-Raf proto-oncogene, serine/threonine kinase inhibitor; LFT = liver function test; CPK = creatine phosphokinase.

Across all checkpoint inhibitors, the median onset of irAEs is typically 5 to 12 weeks after initiation of therapy, but they can occur within days or even hours. They also can occur after months of treatment, or even after discontinuation of therapy, and may affect one or many organs, either concurrently or sequentially. Currently, there are no biomarkers to identify which patients are at risk for which irAEs, or in which sequence.

The incidence and severity of irAEs is higher in anti–CTLA-4 compared to programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) agents. According to Dr. Davies, some research has suggested a dose dependency, as well as a cumulative effect with anti–CTLA-4 agents that is not evident with anti–PD-1/PD-L1 agents. There is also an increase when combined with other immune checkpoint inhibitors, targeted agents, chemotherapy, and radiation therapy (Davies & Duffield, 2017).

Pulmonary Toxicities With Immunotherapy

As an immune-mediated toxicity, patients with lung cancer experience a slightly higher rate of pneumonitis compared to patients with melanoma, renal cell carcinoma, and others that are treated with immune checkpoint inhibitors.

For prevention, smoking cessation and vaccinations are of utmost importance. Patients at risk are those who have received prior chest radiation and those with chronic obstructive pulmonary disease. Patients who have received a TKI and have experienced drug-induced pneumonitis are at an increased risk of developing pneumonitis related to checkpoint inhibitors. Patients typically present with dyspnea, shortness of breath at rest, wheezing, tachypnea/tachycardia, a dry, nonproductive cough, and, very infrequently, chest pain.

Typically, patients with pneumonitis demonstrate a change in oxygen requirements. "The really easy thing to ask patients is, 'Can you walk as far as you used to be able to, can you climb the stairs the way you used to be able to, and do you need to take more frequent breaks in order to accomplish the same tasks?' " Dr. Davies said. Monitoring oxygen saturation, along with respiratory and heart rates, is a quick and inexpensive way to monitor respiratory status. A CT scan is the standard diagnostic imaging required when pneumonitis is suspected.

According to Dr. Davies, if the patient has less than 25% lung involvement (grade 1), continue with immune checkpoint therapy. For 25% to 50% lung involvement (grade 2), hold the immune checkpoint inhibitor; if the patient is hemodynamically unstable, begin steroids with methylprednisolone at 1 to 2 mg/kg per day until the

patient stabilizes. Once the patient has improved to grade 1 or the problem has resolved, begin to taper the steroid over a month. More than 50% lung involvement (grade 3–4) is considered grounds for permanent discontinuation; the patient should also be evaluated for infection and followed up by a pulmonologist. If the patient does not improve within 24 to 48 hours, additional immunosuppressant treatment with infliximab at 5 mg/kg IV should be added, with a second dose in 14 days if needed, she recommended.

Dermatologic Toxicities With Immunotherapy

Dermatologic toxicities are the second most common irAE among patients with lung cancer. Risk factors include underlying dermatologic conditions such as psoriasis or eczema, and prevention is the same as with TKIs: sunscreen, moisturizer, and sunglasses. The first presentation is often significant pruritus. "Patients might say that they feel like they are crawling out of their skin, even if they don't have a rash, but they then will develop a maculopapular rash," she said. If it does progress, rule out other causes such as cellulitis, contact dermatitis, allergies, sun exposure, radiation recall, or other drug reactions.

If the etiology of a rash is unclear, consult dermatology and consider biopsy, she advised. Grading is based on the percentage of surface area covered by the toxicity (grade 1 < 10%, grade 2 = 10% to 30%, grade 3–4 > 30%), but according to Dr. Davies, a rash can be significantly toxic to a patient even if it only covers a small percentage of the body. For grade 1 toxicity, the checkpoint inhibitor can be continued while the patient uses topical steroids and moisturizers. For grade 2, the patient needs a higher-potency topical steroid with or without oral prednisone. For grades 3 to 4, the checkpoint inhibitor should be held and the patient treated topically and systemically with methylprednisolone.

Gastrointestinal and Endocrine Toxicities With Immunotherapy

Common gastrointestinal toxicities include diarrhea and colitis. "Colitis does not always mean that the patient has a significant increase in the number of stools that they have per day," Dr. Davies pointed out. "Think about our lung cancer patients on high doses of opioids who have chronic constipation. An onset of colitis for them might mean they are now going every other day, or maybe once a day, but if it is associated with abdominal cramping, discomfort, spasm or pain, or associated nausea, that could be what colitis looks like for that patient."

Monitoring stool volume is important in managing GI toxicities. Dr. Davies advised that for grade 1 toxicity, consider holding the checkpoint inhibitor and treating with loperamide, and for grade 2, hold treatment and initiate steroids. For grade 3, hold treatment and consider resuming if there is a resolution of symptoms, and for grade 4, permanently discontinue and start the patient on steroids. "A GI consult can be extremely helpful in managing these patients," she added.

Endocrine toxicities involving the thyroid can be significant, but patients may present with vague symptoms such as fatigue, sluggishness, weight loss, or weight gain. Many patients may present with asymptomatic hypothyroid syndrome; therefore, if the thyroid-stimulating hormone (TSH) level is less than 10, it is recommended to continue to monitor thyroid function. If TSH is greater than 10, treatment can be continued, but levothyroxin started. If the TSH and free T4 are low, central hypothyroidism induced by hypophysitis should be considered. In this case, patients will require steroid treatment of hypophysitis. Immune checkpoint inhibitor therapy can be considered after resolution of the hypophysitis.

Adrenal insufficiency is infrequent but can be life-threatening if not identified correctly. It is important to monitor the appropriate lab values to assess for adrenal function (this includes a morning cortisol stimulation test). "One key to adrenal insufficiency is that if you successfully manage these patients with hormone replacement, they can be successfully rechallenged on the immune checkpoint inhibitor," she said, noting that the key is to start corticosteroid hormone replacement prior to any other hormone replacements in order to avoid adrenal crisis.

Many other organ systems can be involved in irAEs (Table 3). It should be noted that the treatment of grade 2 or higher adverse events is methylprednisolone. Immune checkpoint therapy is held or permanently discontinued.

Refractory irAEs and Guiding Principles

Refractory irAEs can also occur in patients on immune checkpoint inhibitors. If there is no improvement in toxicity after the initiation of methylprednisolone, a secondary immunosuppressive agent might be necessary; infliximab is the most common, but is contraindicated in patients who have hepatic involvement or hepatitis, and can reactivate hepatitis B and tuberculosis.

Corticosteroids have not been shown to reduce antitumor efficacy, and are the mainstay of treatment for these patients. As more checkpoint inhibitors are approved, it is important to keep in mind that patients with preexisting autoimmune conditions or organ transplant may be at a higher risk for developing immune-related adverse events. "You have to go down that path cautiously," Dr. Davies said.

Table 3. Presentation and Management of Immune-Related Adverse Events[a]

System	Signs and symptoms	Evaluation	Additional management
Hepatic	Nausea, vague abdominal discomfort, RUQ pain, dehydration, jaundice, bleeding, bruising, dark skin, drowsiness	Liver enzymes (AST, ALT), ALK, total and direct bilirubin, liver ultrasound, GI consult, rule out viral syndrome	Hold hepatotoxic drugs, mycophenolate at 2 mg/kg/day if refractory, no infliximab
Renal, nephritis	Elevated serum creatinine, vague nausea, emesis, decreased urine output, blood in urine, ankle swelling	Serum creatinine, urinalysis, nephrology consult, renal ultrasound, biopsy	Limit nephrotoxic drugs, ABX, NSAIDs, contrast dye, identify high-risk patients (CRF), hydration
Cardiac	Chest pain, SOB, tachycardia, arrhythmias, VTE, fluid retention, pericarditis, myocarditis, effusion, vasculitis	EKG, echocardiogram, CXR, cardiology consult	Blood pressure support, heart rate regulation, permanent discontinuation
Neurologic	Unusual weakness, numbness, peripheral neuropathy, autonomic neuropathy, altered gait, memory difficulties, seizures, aseptic meningitis, myasthenia gravis, Guillain-Barré, encephalitis, transverse myelitis	Neurology consult, MRI of brain to rule out CVA and brain metastases, MRI of spine and LP, rule out infection	Permanent discontinuation, rehab services, IVIG
Ocular	Dry scratchy eyes, vision changes, redness, inflammation, pain, iritis, uveitis, blepharitis, episcleritis, conjunctivitis	Rule out infection, ophthalmology consult	Lubricating eyedrops, topical corticosteroid eyedrops, decrease local irritants such as contact lens or eye makeup
Musculoskeletal	Inflammatory arthritis, myositis, polymyalgia-like syndrome	Rheumatologic tests, autoimmune panel (ANA, RF, anti-CCP, ESR, CK, CRP), imaging, EMG	NSAIDs, corticosteroid joint injections, DMARD, methotrexate, PT/OT
Hematologic	Autoimmune hemolytic anemia, acquired TTP, hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia, acquired hemophilia	CBC, peripheral smear, LDH, haptoglobin, reticulocyte count, DIC panel (PT, PTT), fibrinogen, viral studies (CMV, EBV, HHV6), *ADAMTS13*	RBC or platelet transfusion, growth factor support (if refractory: rituximab, IVIG, cyclosporin, mycophenelate), hematology consult

Note. RUQ = right upper quadrant; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALK = alkaline; GI = gastrointestinal; ABX = antibiotics; NSAID = nonsteroidal anti-inflammatory drug; CRF = chronic renal failure; SOB = shortness of breath; VTE = venous thromboembolism; EKG = electrocardiogram; CXR = chest x-ray; CVA = cerebrovascular accident; LP = lumbar puncture; IVIG = intravenous immunoglobulin; ANA = antinuclear antibody; rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; ESR = erythrocyte sedimentation rate; CK = creatine kinase; CRP = c-reactive protein; EMG = electromyography; DMARD = disease-modifying antirheumatic drug; PT/OT = physical therapy/occupational therapy; TTP = thrombotic thrombocytopenic purpura; CBC = complete blood count; LDH = lactate dehydrogenase, DIC = disseminated intravascular coagulation; PT = prothrombin time; PTT = partial thromboplastin time; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV6 = human herpesvirus 6; RBC = red blood cell.
[a]List is not all inclusive.

Disclosure

Dr. Davies has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Genentech, and Merck. Ms. Eaby-Sandy has served on speakers bureaus for AstraZeneca, Helsinn, Merck, and Takeda, and has served as a consultant for AbbVie.

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