Noninfectious Pneumonitis in a Patient With Renal Cell Carcinoma Treated With Everolimus

Patricia Creel, RN, BSN, OCN®, CCRP, and Nancy P. Moldawer, RN, MSN

A 62-year-old nonsmoking woman named M.B. presented with right upper quadrant pain. An abdominal ultrasound revealed an incidental finding of a large renal mass in her left kidney. She underwent a hand-assisted laparoscopic left nephrectomy for a 7.5 cm tumor (T2 [tumor more than 7 cm], Fuhrman grade 3, clear-cell renal cell carcinoma [RCC]) with negative surgical margins; the renal vein was disease-free. Postoperative care included routine surveillance with computed tomography (CT) scans of the chest, abdomen, and pelvis every six months.

One year postnephrectomy, M.B. returned with new left-side upper back pain and mild fatigue. A chest CT scan demonstrated a soft tissue mass in the left lung apex with destruction of the left posterior second rib and multiple pulmonary lesions (1–2.5 cm). She was started on sunitinib (daily dosing for four weeks, followed by a two-week rest) and a bisphosphonate. M.B. initially responded to therapy and achieved a 30% tumor-size reduction. After 10 months, however, she demonstrated progressive disease with growing pulmonary and liver lesions. Treatment was switched to everolimus 10 mg per day according to the National Comprehensive Cancer Network's ([NCCN], 2010) clinical practice guidelines, and M.B. had stable disease following three months of treatment.

At a regularly scheduled visit four months after initiating everolimus, M.B. presented with shortness of breath and dry cough (gradually increasing over the prior two weeks), oxygen saturation of 90% on room air, and a chest x-ray demonstrating bilateral interstitial infiltrates. She complained of worsening fatigue that, combined with dyspnea, limited her mobility. M.B. was afebrile and denied having fever or chills. Everolimus was withheld and she was admitted to the hospital. A chest CT scan demonstrated diffuse ground-glass opacities (see Figure 1). Pulmonary function tests revealed diminished diffusing capacity of the lungs. M.B. was treated empirically with corticosteroids (prednisone 60 mg per day) and oxygen. A pulmonary consult was obtained, and a bronchoscopy with cultures was performed to rule out infection. The pneumonitis grading criteria within the National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events, version 4.0, is based on the severity of symptoms, degree of impact on activities of daily living, and the type of intervention required. In this case, a diagnosis of grade 3 noninfectious pneumonitis was made.

After a three-day hospital stay, M.B. was discharged on supplemental oxygen and a steroid taper. Within a week, she had no shortness of breath at rest and did not require supplemental oxygen. Two weeks after discharge, a chest radiograph showed resolving opacities bilaterally; her dyspnea and fatigue had returned to baseline, and she had completed the steroid taper. Everolimus was reintroduced at 5 mg per day following resolution of pneumonitis to grade 1. M.B. was scheduled for biweekly visits for the first month after continuing therapy, with monthly chest x-rays and blood tests. Everolimus therapy was continued for an additional three months without evidence of recurrent pneumonitis until restaging revealed progressive disease with new liver lesions.

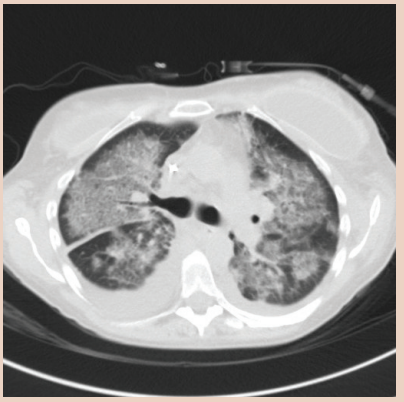

Figure 1. Chest Computed Tomography Scan Showing Diffuse Ground-Glass Opacities

Note. Image courtesy of Duke University Medical Center. Used with permission.

Noninfectious Pneumonitis

M.B. initiated everolimus 10 mg per day after failing sunitinib, consistent with the U.S. Food and Drug Administration-approved dosing and indication of everolimus (Novartis Pharmaceuticals Corporation, 2009). Approval was based on the phase III RECORD-1 trial (Hudes, 2010) in which patients with metastatic RCC treated with sunitinib or sorafenib were randomized to receive everolimus 10 mg per day or placebo. Clinical benefit was observed, with 67% of everolimus recipients maintaining stable disease (with one partial response) versus 32% of placebo recipients, translating into a highly significant difference in progression-free survival (4.9 versus 1.9 months; $p < 0.001$) (Motzer et al., 2010). Stomatitis, infections, and asthenia or fatigue were the most prominent toxicities when considering all grades, including grade 3–4 events. Noninfectious pneumonitis occurred in 14% of patients receiving everolimus; 4% had grade 3 and no one reported grade 4 events (Motzer et al., 2010).

Noninfectious pneumonitis is a class effect of mammalian target of rapamycin (mTOR) inhibitors, initially reported with rapamycin or sirolimus for antirejection in organ transplantation recipients (Lennon, Finan, FitzGerald, & McCormick,

Table 1. Management Recommendations for Everolimus-Associated Pneumonitis

Description	Intervention
Grade 1: Asymptomatic	No specific treatment
Grade 2: Symptomatic, but not interfering with activities of daily living	Consider corticosteroid therapy. Decrease everolimus dose until the grade is 1 or lower, hold everolimus if symptoms are troublesome and, if no recovery to grade 1 occurs within three weeks, discontinue everolimus.
Grade 3: Symptomatic, interfering with activities of daily living	Consider corticosteroid therapy. Hold everolimus until recovery to grade 1 and restart the dose within two weeks at reduced dose (5 mg per day) based on evidence of clinical benefit.
Grade 4: Life-threatening, ventilatory support indicated	Consider corticosteroid therapy and discontinue everolimus treatment.

Note. Based on information from Hudes, 2010; National Cancer Institute, 2006; Novartis Pharmaceuticals Corporation, 2009.

2001; Morelon et al., 2001), and more recently with the newer rapamycin analogs (e.g., temsirolimus, everolimus, ridaforolimus) for treatment of cancer (Amato, Jac, Giessinger, Saxena, & Willis, 2009; Atkins et al., 2004; Bellmunt, Szczylik, Feingold, Strahs, & Berkenblit, 2008; Duran, Siu, et al., 2006; Motzer et al., 2010). The incidence of pneumonitis in clinical trials of mTOR inhibitor anticancer monotherapy has been as low as 2% (in a large, phase-III trial in advanced poor-prognosis RCC), although it exceeded 30% in several series and approached 50% in a small, phase-II trial in metastatic clear-cell RCC (Amato et al., 2009; Atkins et al., 2004; Bellmunt et al., 2008; Duran, Siu, et al., 2006; Motzer et al., 2010). The wide range of incidences may reflect differences in the frequency and type of imaging studies performed or dosing and duration of mTOR inhibitor therapy (Sankhala et al., 2009). Typically pneumonitis had been of grades 1–2 in severity and reversible (Ellard et al., 2009), with consistently low mortality rates.

Patients with preexisting pulmonary dysfunction or poor performance status have a heightened propensity for developing pulmonary toxicity during cancer-directed therapy (Vahid & Marik, 2008). The mechanism whereby mTOR inhibitors induce noninfectious pneumonitis has not yet been elucidated. Some researchers have argued that mTOR inhibitor-induced pneumonitis reflects a cell-mediated autoimmune response (Morelon et al., 2001); others have proposed that it may represent a T-cell mediated, delayed-type hypersensitivity reaction (Pham et al., 2004). The impact of dose is likewise uncertain. Whereas transplantation studies demonstrated dose dependency for rapamycin-associated pneumonitis (Morelon et al., 2001; Pham et al., 2004), clinical experiences generally have not supported mTOR inhibitor-induced noninfectious pneumonitis as dose-related (Duran, Kortmansky, et al., 2006). The extent to which prior chest radiation increases the risk of mTOR inhibitor-induced noninfectious pneumonitis is unclear, although a clinical study of patients with metastatic or recurrent breast cancer suggests that it may be an influencing factor (Ellard et al., 2009).

Challenges of Diagnosing Pneumonitis

Given the inherently complex, often multifactorial etiology of pulmonary compromise in patients with cancer, mTOR inhibitor-induced noninfectious pneumonitis has substantial potential for misdiagnosis (Sankhala et al., 2009). In addition, the immunosuppressive properties of mTOR inhibitors (Thomson, Turnquist, & Raimondi, 2009) predispose patients to opportunistic infections and add to the complexity of determining the cause of new-onset respiratory symptoms. A diagnosis of noninfectious pneumonitis should follow an exclusionary approach and is ultimately based on clinical judgment (Novartis Pharmaceuticals Corporation, 2009).

Noninfectious pneumonitis should be included in the differential diagnosis of patients treated with mTOR inhibitors presenting with nonspecific respiratory symptoms (Novartis Pharmaceuticals Corporation, 2009). Ruling out infectious, malignant, and other treatment-related etiologies is critical (Sankhala et al., 2009), warranting a comprehensive work-up that may include CT scans or x-rays, pulmonary function tests (e.g., spirometry, diffusion capacity, room air oxygen saturation at rest), and diagnostics to exclude infection (e.g., bronchoscopy, cultures). Considering the potential confounding impact of preexisting pulmonary abnormalities, baseline lung imaging prior to instituting mTOR inhibitor therapy and routine pulmonary function testing has been proposed to facilitate interpretation of radiographic imaging performed in response to treatment-emergent respiratory symptoms (Sankhala et al., 2009).

The typical onset of mTOR inhibitor-induced noninfectious pneumonitis has been within 4–6 months of initiating therapy (Duran, Kortmansky, et al., 2006; Ellard et al., 2009; Pham et al., 2004), with patients developing evidence of radiographic changes with or without other accompanying symptoms of pulmonary compromise (e.g., pleural effusion, hypoxia, cough, dyspnea, malaise) (Duran, Kortmansky, et al., 2006; Sankhala et al., 2009). Drug-induced noninfectious pneumonitis also has been associated with fever and fatigue (Champion et al., 2006; Duran, Kortmansky, et al., 2006). Based on a review of medical and radiographic data for patients across two clinical trials of temsirolimus focused on characterizing noninfectious pneumonitis, two different radiologic patterns were apparent: ground-glass opacities with or without diffuse interstitial disease and lung parenchymal consolidation (Duran, Kortmansky, et al., 2006).

Clinical Management

Drug-induced pneumonitis may follow a relatively indolent course or present as (or develop into) a rapidly progressive, potentially fatal condition resulting in acute respiratory distress syndrome and respiratory failure (Vahid & Marik, 2008). To date, no specific management guidelines exist for mTOR inhibitor–induced noninfectious pneumonitis. The extent of radiographic abnormalities and symptom severity represent key factors in determining the need for intervention (i.e., interruption of mTOR inhibition, implementation of corticosteroids, and intensive supportive measures in severe cases) (Novartis Pharmaceuticals Corporation, 2009; Vahid & Marik, 2008). Management recommendations based

Before initiating mTOR-inhibitor therapy:

- Obtain complete medical history, with an emphasis on pulmonary conditions.
- Perform a baseline chest x-ray or computed tomography scan to document pulmonary status if the patient has respiratory symptoms prior to therapy.
- Remember that noninfectious pneumonitis can occur with or without signs or symptoms and that, although rare, a fatal outcome with noninfectious pneumonitis has been observed.
- Advise patients to promptly report any new or worsening respiratory symptoms (e.g., cough, shortness of breath).
- Note that onset generally occurs within two to six months of initiating therapy.

In the event of symptoms suggestive of noninfectious pneumonitis:

- The diagnosis of noninfectious pneumonitis is complicated and requires that other diagnoses be ruled out, such as infections, pulmonary thromboembolism, alveolar hemorrhage, tumor progression, and other medical conditions.
- Patients who develop radiologic changes suggestive of noninfectious pneumonitis and who have few symptoms may continue therapy without dose modification.
- If symptomatic noninfectious pneumonitis develops, consider consulting a pulmonologist, treating with corticosteroids, and modifying treatment using dose modification or interruption guidelines.

mTOR—mammalian target of rapamycin

Figure 2. Key Points for Nurses Treating Noninfectious Pneumonitis

Note. Based on information from Hudes, 2010.

on the RECORD-1 trial and accumulated clinical experience are summarized in Table 1. Patients with radiologic evidence of noninfectious pneumonitis, who are asymptomatic or have few symptoms, may continue everolimus without dose adjustment (Novartis Pharmaceuticals Corporation, 2009).

When outlining the known risks and benefits of mTOR inhibitor therapy to patients, potential compromising respiratory and immunologic effects should be discussed with the goal of promoting early detection. The potentially serious but generally manageable nature of noninfectious pneumonitis should be explained, as should the benefits of vigilance (see Figure 2). The importance of prompt reporting of any new or worsening respiratory symptoms cannot be overstated and should be emphasized for patients and caregivers, not only at the onset of therapy but also during routine follow-up.

Patricia Creel, RN, BSN, OCN®, CCRP, is a clinical research associate, senior lead, at Duke University Medical Center in Durham, NC, and Nancy P. Moldawer, RN, MSN, is a research clinical trials program coordinator in the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles, CA. Editorial assistance was provided by Scientific Connexions in Newtown, PA, and funded by Novartis Pharmaceuticals. Creel can be reached at patricia.creel@duke.edu, with copy to editor at ONFEditor@ons.org.

Digital Object Identifier: 10.1188/11.ONF.125-128

References

Amato, R.J., Jac, J., Giessinger, S., Saxena, S., & Willis, J.P. (2009). A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. *Cancer, 115,* 2438–2446. doi: 10.1002/cncr.24280

Atkins, M.B., Hidalgo, M., Stadler, W.M., Logan, T.F., Dutcher, J.P., Hudes, G.R., . . . Sherman, M.L. (2004). Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *Journal of Clinical Oncology, 22,* 909–918. doi: 10.1200/JCO.2004.08.185

Bellmunt, J., Szczylik, C., Feingold, J., Strahs, A., & Berkenblit, A. (2008). Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. *Annals of Oncology, 19,* 1387–1392. doi: 10.1093/annonc/mdn066

Champion, L., Stern, M., Israël-Biet, D., Mamzer-Bruneel, M.F., Peraldi, M.N., Kreis, H., . . . Morelon, E. (2006). Brief communication: Sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Annals of Internal Medicine, 144,* 505–509.

Duran, I., Kortmansky, J., Singh, D., Hirte, H., Kocha, W., Goss, G., . . . Siu, L.L. (2006). A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *British Journal of Cancer, 95,* 1148–1154. doi: 10.1038/sj.bjc.6603419

Duran, I., Siu, L.L., Oza, A.M., Chung, T.B., Sturgeon, J., Townsley, C.A., . . . Niroumand, M. (2006). Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *European Journal of Cancer, 42,* 1875–1880. doi: 10.1016/j.ejca.2006.03.015

Ellard, S.L., Clemons, M., Gelmon, K.A., Norris, B., Kennecke, H., Chia, S., . . . Seymour, L. (2009). Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. *Journal of Clinical Oncology, 27,* 4536–4541.

Hudes, G. (2010). Pulmonary toxicity of the rapamycin analog class of mTOR inhibitors. *Kidney Cancer Journal, 8,* 21–24.

Lennon, A., Finan, K., FitzGerald, M.X., & McCormick, P.A. (2001). Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation, 72,* 1166–1167. doi: 10.1097/00007890-200109270-00034

Morelon, E., Stern, M., Israël-Biet, D., Correas, J.M., Danel, C., Mamzer-Bruneel, M.F. . . . Kreis, H. (2001). Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation, 72,* 787–790. doi: 10.1097/00007890-200109150-00008

Motzer, R.J., Escudier, B., Oudard, S., Hutson, T.E., Porta, C., Bracarda, S., . . . Ravaud, A. (2010). Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. *Cancer, 116,* 4256–4265. doi: 10.1002/cncr.25219

National Cancer Institute. (2006). *Common Terminology Criteria for Adverse Events* [v.3.0]. Retrieved from http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

National Cancer Institute. (2010). *Common Terminology Criteria for Adverse Events* [v.4.0]. Retrieved from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

National Comprehensive Cancer Network. (2010). *Clinical Practice Guidelines in Oncology™: Kidney cancer* [v.2.2010]. Retrieved from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

Novartis Pharmaceuticals Corporation. (2009). *Afinitor®* [Prescribing information]. East Hanover, NJ: Author.

Pham, P.T., Pham, P.C., Danovitch, G.M., Ross, D.J., Gritsch, H.A., Kendrick, E.A., . . . Wilkinson, A.H. (2004). Sirolimus-associated pulmonary toxicity. *Transplantation, 77,* 1215–1220.

Sankhala, K., Mita, A., Kelly, K., Mahalingam, D., Giles, F., & Mita, M. (2009). The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. *Targeted Oncology, 4,* 135–142. doi: 10.1007/s11523-009-0107-z

Thomson, A.W., Turnquist, H.R., & Raimondi, G. (2009). Immunoregulatory functions of mTOR inhibition. *Nature Reviews Immunology, 9,* 324–337. doi: 10.1038/nri2546

Vahid, B., & Marik, P.E. (2008). Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest, 133,* 528–538.

Clinical Highlights: Noninfectious Pneumonitis and mTOR Inhibitors

Definition

Noninfectious pneumonitis is a class effect of the mammalian target of rapamycin (mTOR) inhibitors (e.g., temsirolimus, everolimus, ridaforolimus) undergoing extensive evaluation for treatment of cancer (Duran, Kortmansky, et al., 2006; Duran, Siu, et al., 2006; Ellard et al., 2009). The incidence of pneumonitis in published clinical trials of mTOR inhibition as anticancer monotherapy has been reported to be as low as 2% and as high as 50%; events typically have been of grades 1 or 2 in severity and reversible, with consistently low mortality rates.

The pneumonitis grading criteria within the National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events, version 4.0, is based on the severity of symptoms, degree of impact on activities of daily living, and the type of intervention required. Typical onset of mTOR inhibitor-induced noninfectious pneumonitis has been within 4–6 months of initiating therapy, with patients developing evidence of radiographic changes with or without other accompanying signs and symptoms of pulmonary compromise (Duran, Kortmansky, et al., 2006; Duran, Siu, et al., 2006; Ellard et al., 2009; Pham et al., 2004; Sankhala et al., 2009). Drug-induced pneumonitis may follow a relatively indolent course or present as, or develop into, a rapidly progressive, potentially fatal condition resulting in acute respiratory distress syndrome (grade 4 severity) and respiratory failure (Vahid & Marik, 2008).

Pathophysiology

The underlying cause of noninfectious pneumonitis has not yet been determined. Proposed mechanisms whereby mTOR inhibitors induce noninfectious pneumonitis include drug-induced cell-mediated autoimmune response (Morelon et al., 2001) or a T-cell mediated, delayed-type hypersensitivity reaction (Pham et al., 2004). The impact of dose on the development of this complication is likewise uncertain. Although studies in organ transplantation settings demonstrated dose dependency for rapamycin-associated pneumonitis (Morelon et al., 2001; Pham et al., 2004), clinical experiences with the rapamycin analogs in patients with cancer have found that mTOR inhibitor-induced noninfectious pneumonitis is not a dose-related phenomenon (Duran, Kortmansky, et al., 2006). A clinical study in patients with metastatic or recurrent breast cancer suggested that chest radiation may be an influencing factor (Ellard et al., 2009), although the extent to which prior radiation to the chest increases the risk is unknown.

Treatment

As with drug-induced pneumonitis irrespective of the causative treatment type, the extent of radiographic abnormalities and the severity and debilitating nature of symptoms represent the key factors for driving decisions regarding the need for intervention (Novartis Pharmaceuticals Corporation, 2009; Vahid & Marik, 2008). Management recommendations based on the RECORD-1 trial protocol and the accumulated clinical experience from patients treated with mTOR inhibitors are dependent on severity (Hudes, 2010; Novartis Pharmaceuticals Corporation, 2009). According to everolimus' approved prescribing information, patients with radiologic evidence of noninfectious pneumonitis who are asymptomatic or have few symptoms may continue everolimus therapy without dose adjustment (Novartis Pharmaceuticals Corporation, 2009). Interruption of mTOR inhibitor and corticosteroid therapy should be considered if symptoms are moderate or severe; after recovery, treatment may be reinitiated at 5 mg per day. If no recovery to grade 1 or lower occurs within three weeks, treatment should be discontinued. For grade 4 noninfectious pneumonitis, treatment discontinuation is recommended.

Nursing Implications

Before initiating mTOR inhibitor therapy, a complete medical history, with an emphasis on pulmonary conditions, should be obtained. Patients with a history of pulmonary conditions should be carefully monitored, and patients should be advised to promptly report any new or worsening respiratory symptoms. When outlining the known risks and benefits of mTOR inhibitor therapy from a patient education perspective, the potential compromising respiratory and immune system effects are a fundamental area of discussion, with the overarching goal of promoting early detection in the interval between follow-up visits. The potentially serious but generally manageable nature of noninfectious pneumonitis should be explained, as should the benefits of vigilance on the part of the patient and caregivers.

References

Duran, I., Kortmansky, J., Singh, D., Hirte, H., Kocha, W., Goss, G., . . . Siu, L.L. (2006). A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *British Journal of Cancer, 95,* 1148–1154.

Duran, I., Siu, L.L., Oza, A.M., Chung, T.B., Sturgeon, J., Townsley, C.A., . . . Niroumand, M. (2006). Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *European Journal of Cancer, 42,* 1875–1880.

Ellard, S.L., Clemons, M., Gelmon, K.A., Norris, B., Kennecke, H., Chia, S., . . . Seymour, L. (2009). Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. *Journal of Clinical Oncology, 27,* 4536–4541.

Hudes, G. (2010). Pulmonary toxicity of the rapamycin analog class of mTOR inhibitors. *Kidney Cancer Journal, 8,* 21–24.

Morelon, E., Stern, M., Israël-Biet, D., Correas, J.M., Danel, C., Mamzer-Bruneel, M.F., . . . Kreis, H. (2001). Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation, 72,* 787–790.

National Cancer Institute. (2010). *Common Terminology Criteria for Adverse Events* [v.4.0]. Retrieved from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Novartis Pharmaceuticals Corporation. (2009). *Afinitor®* [Prescribing information]. East Hanover, NJ: Author.

Pham, P.T., Pham, P.C., Danovitch, G.M., Ross, D.J., Gritsch, H.A., Kendrick, E.A., . . . Wilkinson, A.H. (2004). Sirolimus-associated pulmonary toxicity. *Transplantation, 77,* 1215–1220.

Sankhala, K., Mita, A., Kelly, K., Mahalingam, D., Giles, F., & Mita, M. (2009). The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. *Targeted Oncology, 4,* 135–142.

Vahid, B., & Marik, P.E. (2008). Pulmonary complications of novel antineoplastic agents. *Chest, 133,* 528–538.