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Drug-Related Pneumonitis in Patients With Advanced Renal Cell Carcinoma Treated With Temsirolimus

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ABSTRACT

Purpose
Pneumonitis has occurred in patients treated with inhibitors of the mammalian target of rapamycin (mTOR). In a phase III study of patients with previously untreated, poor-prognosis, advanced renal cell carcinoma (ARCC), the mTOR inhibitor temsirolimus improved survival compared with interferon. We performed a retrospective, independent, blinded radiographic review of chest computed tomography (CT) images of patients in this study to characterize temsirolimus-related pneumonitis.

Patients and Methods
Patients were treated with intravenous temsirolimus 25 mg once weekly or subcutaneous interferon alfa 3 million units, with an increase to 18 million units, thrice weekly. Drug-related pneumonitis was identified based on sequential chest CT images, required every 8 weeks, showing changes consistent with pneumonitis and not pneumonia (infection) or disease progression as correlated with clinical data. Cumulative probability of drug-related pneumonitis was estimated using the Kaplan-Meier method.

Results
Eight (6%) of 138 and 52 (29%) of 178 evaluable patients on interferon and temsirolimus treatment, respectively, developed radiographically identified drug-related pneumonitis. Time to onset of pneumonitis was significantly shorter on the temsirolimus arm than on the interferon arm (log-rank $P < .001$). Estimated cumulative probability of pneumonitis at 8 and 16 weeks from first dose was 21% and 31%, respectively, on the temsirolimus arm and 6% and 8%, respectively, on the interferon arm. Respiratory symptoms were observed around time of onset of radiographically diagnosed temsirolimus-related pneumonitis in 16 (31%) of 52 patients.

Conclusion
Patients with ARCC receiving temsirolimus should be monitored closely for development of pneumonitis, and their management should be altered if clinical symptoms appear.

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INTRODUCTION

Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR), with proven efficacy in advanced renal cell carcinoma (ARCC). In a randomized first-line phase III trial, temsirolimus increased overall survival compared with interferon in patients with poor-prognosis ARCC.[1] In this global ARCC trial and in earlier phase I and II trials (761 total patients), the most common adverse events with temsirolimus monotherapy were fatigue/asthenia, rash, anemia, and mucositis/stomatitis.[2] Drug-related pneumonitis has been reported in 2% to 36% of patients receiving temsirolimus.[3-7] In the global ARCC trial, investigators identified 2% of patients (four of 208 patients) as having temsirolimus-related pneumonitis.[3] Pulmonary radiographic patterns and the clinical significance of this complication are largely unknown.

To more accurately analyze the incidence of temsirolimus-related pneumonitis and identify radiographic patterns, an independent radiologist performed a retrospective, blinded review of chest computed tomography (CT) images from patients with poor-prognosis ARCC who were treated with temsirolimus (n = 208) or interferon (n = 200) in the global ARCC trial.

PATIENTS AND METHODS

Study Design

The primary objective of this analysis was to examine the association between treatment and development of

drug-related pneumonitis as identified by independent, retrospective radiographic review of chest CT images of patients in the global ARCC trial. Secondary objectives were to characterize the radiographic spectrum of drug-related pneumonitis and the respiratory symptoms associated with its development.

In the global ARCC trial, patients with previously untreated, poor-prognosis ARCC were randomly assigned to receive temsirolimus alone, interferon alone, or the combination of temsirolimus and interferon.[1] Temsirolimus, but not the combination, showed a statistically significant improvement in the primary end point of overall survival compared with interferon. Thus, single-agent temsirolimus is approved for the treatment of ARCC in the United States and Europe.[8] In this analysis, the prevalence of drug-related pneumonitis detected from chest CT images was compared between the temsirolimus alone and interferon alone treatment groups to provide information about drug-related pneumonitis when temsirolimus is used as approved. Chest CT images of patients in the combination group were not included in the independent, retrospective review.

Patients

Patients were required to have histologically confirmed ARCC (stage IV or recurrent disease); a measurable tumor according to Response Evaluation Criteria in Solid Tumors (RECIST)[9]; no prior systemic therapy; a Karnofsky performance score of ≥ 60; and adequate renal, hepatic, and bone marrow function.[1] Patients had to have at least three of the following six poor prognostic factors: serum lactate dehydrogenase levels greater than 1.5× the upper limit of the normal range; hemoglobin levels less than the lower limit of normal range; corrected serum calcium greater than 10 mg/dL; less than 1 year from initial renal cell cancer diagnosis to random assignment; Karnofsky performance score of 60 or 70; and multiple organ sites of metastases.

The study protocol was approved by the institutional review boards of the participating institutions and was conducted in a manner consistent with international standards of good clinical practice. All patients gave written informed consent.

Treatment

Patients in the interferon group received interferon alfa-2a (Roferon-A; Hoffman-La Roche, Nutley, NJ) at a dose of 3 million units subcutaneously three times per week for the first week, with escalation to 18 million units or the highest tolerable dose three times per week. Patients in the temsirolimus group received temsirolimus (Torisel; Pfizer, Philadelphia, PA) 25 mg as a 30-minute intravenous infusion once weekly. Intravenous diphenhydramine 25 to 50 mg or a similar H_1 blocker was given approximately 30 minutes before each temsirolimus infusion to minimize the risk of acute hypersensitivity reaction.

Study Evaluation

CT scans of the chest, abdomen, and pelvis were obtained before treatment and at 8-week intervals during treatment for assessment of tumor burden, until disease progression. Radiographic evaluations continued at 8-week intervals for patients discontinuing treatment for reasons other than disease progression or initiation of new cancer therapy. Patients were evaluable for radiographic review to identify pulmonary abnormalities if they had chest CT images at baseline without pulmonary abnormalities consistent with pneumonitis and had at least one postbaseline evaluation.

Sequential chest CT images were read in an independent, blinded review. The independent radiologist (C.S.W.) was blinded to the treatment group of each patient and to clinical data, including adverse events and tumor progression. Each CT image was evaluated for the following: image quality (optimal, readable not optimal, or unreadable); presence of lobar involvement; percentage of involvement and degree of severity ($< 25\%$ involvement as minimal severity; $\geq 25\%$ to $< 50\%$ as mild; $\geq 50\%$ to $< 75\%$ as moderate; or $\geq 75\%$ as severe); distribution of disease (peripheral, diffuse, central, or mixed) for each of six lung locations (right upper lobe, right middle lobe, right lower lobe, lingula, left upper lobe excluding lingula, and left lower lobe); and eight types of observations (bronchiectasis, consolidation, reticular opacities, ground glass opacities, nodular pattern, mosaic attenuation, honeycombing, and other).[10] Each postbaseline CT image was compared with the previous image, and pulmonary status was reported as no change, worsening (any change from one degree of severity to a more severe one), or improvement (any change from one degree of severity to a less severe one).

On the basis of examination of sequential CT images, the independent radiologist noted whether the pulmonary abnormalities observed were likely caused by pneumonitis, pneumonia, or metastases. For patients in whom pulmonary abnormalities were suspected to be pneumonia or metastases from CT images, the sponsor reviewed clinical data, without consideration of treatment assignment, to confirm or rule out the suspected abnormality.

Statistical Methods

Cumulative probability of developing drug-related pneumonitis was estimated using the Kaplan-Meier method. Patients without worsening status were censored on the last chest CT examination date in the database. The time point–specific cumulative probability and its 95% CI were estimated using log-log transformation. Time points included points that corresponded to the first and second protocol-scheduled tumor assessment times (8 and 16 weeks) and 13 months (after last event in database). Time to onset of drug-related pneumonitis (defined as the duration from date of first dose to date of first chest CT examination wherein status was reported to have worsened from baseline) was compared between treatment groups using the log-rank test.

RESULTS

Association Between Treatment and Drug-Related Pneumonitis

In this phase III trial, patients with poor-prognosis ARCC were randomly assigned and treated with interferon (n = 200) or temsirolimus (n = 208; Fig 1). Of these, 138 patients who received interferon and 178 patients who received temsirolimus were evaluable for retrospective, radiographic review of chest CT images. Patients were nonevaluable for this review because of missing screening or postbaseline images (interferon, n = 55; temsirolimus, n = 17), unreadable images (interferon, n = 4; temsirolimus,

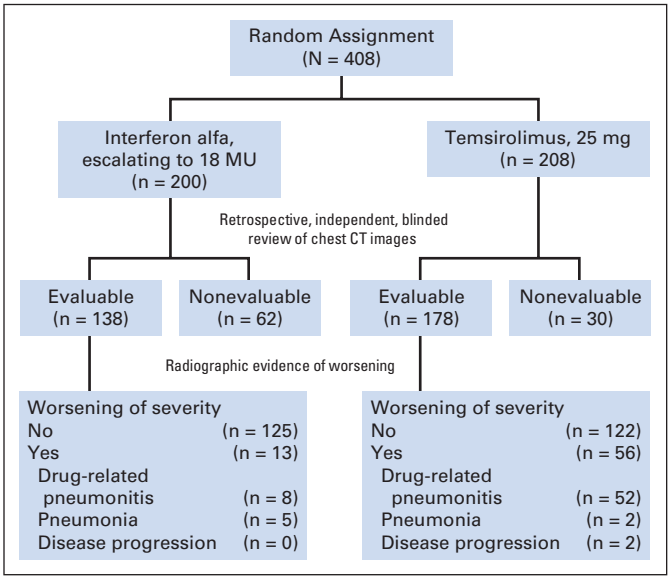

Fig 1. Analysis of patients with poor-prognosis advanced renal cell carcinoma who were treated with interferon alfa or temsirolimus to identify patients with radiographically diagnosed drug-related pneumonitis. MU, million units; CT, computed tomography.

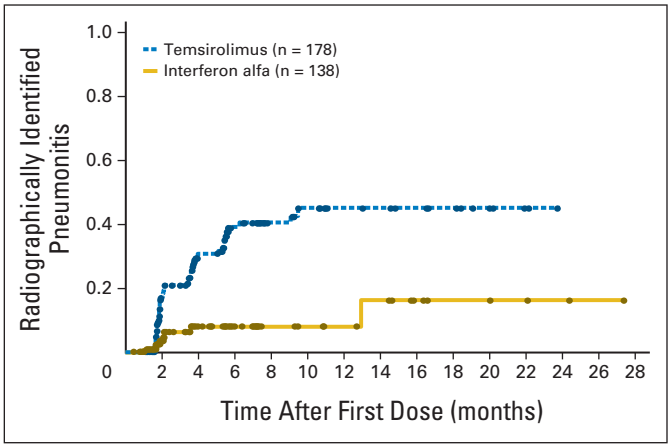

Fig 2. Cumulative probability of radiographically identified drug-related pneumonitis in patients treated with interferon alfa or temsirolimus (log-rank $P < .001$). Circles represent censored observations (patients without worsening status on the last chest computed tomography examination date in the database).

n = 7), or radiographic pulmonary abnormalities consistent with pneumonitis at baseline (interferon, n = 3; temsirolimus, n = 6). More patients in the interferon group had missing postbaseline CT images because a greater percentage experienced disease progression or symptomatic deterioration before the first protocol-specified postbaseline tumor assessment.

Eight (6%) and 52 (29%) instances of drug-related pneumonitis were identified in evaluable patients on interferon and temsirolimus, respectively, after radiographic review of all CT images and correlation of clinical data for patients with CT images suggestive of pneumonia or disease progression. The Kaplan-Meier estimated cumulative probability of developing drug-related pneumonitis in the two treatment arms is shown in Figure 2.

Time to onset of radiographically diagnosed pneumonitis was significantly shorter in the temsirolimus group than in the interferon group (log-rank $P < .001$). In the temsirolimus arm, the estimated cumulative probability of radiologically identified drug-related pneumonitis was 21% (95% CI, 15% to 29%) at 8 weeks, 31% (95% CI, 24% to 40%) at 16 weeks, and 45% (95% CI, 36% to 57%) at 13 months. In the interferon arm, the cumulative probability was 6% (95% CI, 3% to 14%) at 8 weeks, 8% (95% CI, 4% to 17%) at 16 weeks, and 16% (95% CI, 6% to 42%) at 13 months.

Figure 3 shows examples of CT images of patients who had pneumonitis and pneumonia. In this report, we will characterize the temsirolimus-related pneumonitis and not the interferon-related pneumonitis that occurred in patients with poor-prognosis ARCC. Interferon-related pneumonitis has been described previously.[11]

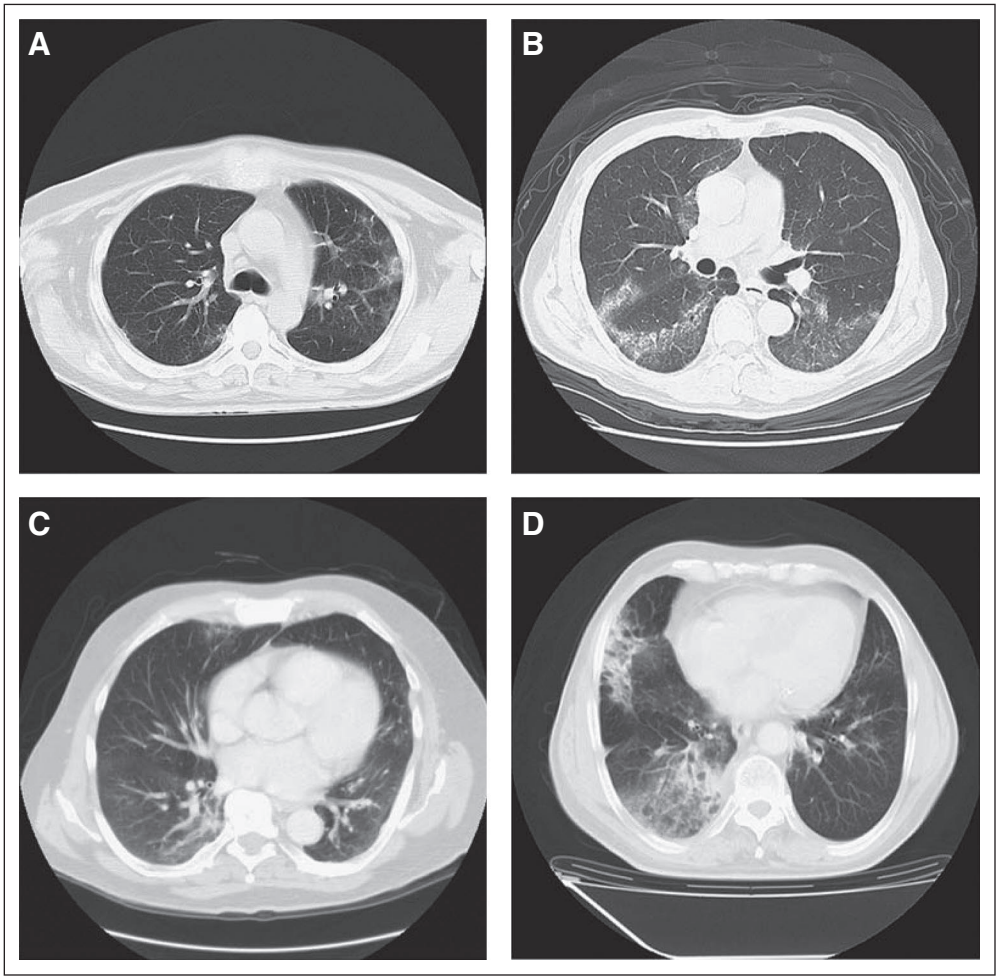

Fig 3. Computed tomography (CT) images obtained on lung windows of patients with (A, B, and C) temsirolimus-related pneumonitis and (D) pneumonia. (A) A 52-year-old man with drug-related pneumonitis. CT image obtained at study week 24 shows ground glass opacity that involves the lateral left upper lobe and, to a lesser extent, the posterior right upper lobe. (B) A 69-year-old man with drug-related pneumonitis. CT image obtained at study week 8 shows ground glass opacity that involves the posterior lungs, predominantly the superior segments of both lower lobes. (C) A 67-year-old man with drug-related pneumonitis. CT image obtained at study week 8 shows a cluster of reticular opacities in the right upper lobe. (D) A 61-year-old man with pneumonia. CT image obtained at study week 40 shows areas of consolidation containing scattered lucencies in the right middle and lower lobes. The CT images in (A), (B), and (C) were considered clinically consistent with pneumonitis in the absence of other symptoms.

Table 1. Radiographic Abnormalities Observed for Patients With Temsirolimus-Related Pneumonitis

Abnormality	No. of Patients (n = 52)	%
Ground glass opacities but not consolidation		
Ground glass opacities only	16	31
Ground glass opacities, nodular pattern	2	4
Ground glass opacities, reticular opacities	1	2
Consolidation but not ground glass opacities		
Consolidation only	10	19
Consolidation, nodular pattern	1	2
Consolidation, reticular opacities	3	6
Ground glass opacities and consolidation		
Ground glass opacities, consolidation	17	33
Ground glass opacities, consolidation, reticular opacities	1	2
Neither ground glass opacities nor consolidation		
Nodular pattern	1	2

Table 2. Treatment-Emergent Respiratory Symptoms Associated With the Onset of Temsirolimus-Related Pneumonitis

Adverse Event*	No. of Patients (n = 52)†	%
Any respiratory symptom	16	31
Increased cough	8	15
Dyspnea	6	12
Pneumonitis	2	4
Hemoptysis	2	4
Upper respiratory infection	2	4
Bronchitis	1	2
Pulmonary physical finding	1	2

*Respiratory adverse events were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) and occurred between 8 weeks before and 4 weeks after the date of first onset of temsirolimus-related pneumonitis as identified by radiographic review of chest computed tomography images.
†A patient could have more than one adverse event.

Characterization of Temsirolimus-Related Pneumonitis

The proportion of patients who had radiographically diagnosed drug-related pneumonitis in the temsirolimus group was similar between men (31%, 36 of 118 men) and women (26%, 16 of 61 women) and across geographic regions (United States: 30%, 14 of 47 patients; Australia, Canada, and Western Europe: 31%, 12 of 39 patients; Africa, Asia Pacific, Eastern Europe, and South America: 28%, 26 of 92 patients).

The abnormalities consistent with drug-related pneumonitis observed by the independent, retrospective review of patients with CT images are listed in Table 1. Ground glass opacities and consolidation, either alone or in combination, were the most commonly observed abnormalities. These abnormalities often involved multiple lobes; 95% of patients (35 of 37 patients) with ground glass opacities had involvement of multiple lobes, and 72% of patients (23 of 32 patients) with consolidation had involvement of multiple lobes.

Review of chest CT images indicated that onset of drug-related pneumonitis occurred within the first 8 weeks of temsirolimus treatment in 60% of patients (31 of 52 patients). Similar proportions of the remaining patients had onset after 8 weeks and within 16 weeks of temsirolimus treatment (21%, 11 of 52 patients) and after 16 weeks of temsirolimus treatment (19%, 10 of 52 patients). Exploratory analysis of duration of radiographic changes consistent with temsirolimus-related pneumonitis was attempted but was hampered by the retrospective nature of the study; the study protocol required CT scans only until disease progression. Follow-up CT scans were often not available because many patients discontinued treatment as a result of disease progression after the first or second scan.

Respiratory Symptoms Associated With Temsirolimus-Related Pneumonitis

Treatment-emergent respiratory symptoms that occurred with an onset date between 8 weeks before and 4 weeks after the onset date of temsirolimus-related pneumonitis, as identified by radiographic review of chest CT images, were considered associated with the onset of the pneumonitis. Respiratory symptoms were associated with onset of radiographically diagnosed temsirolimus-related pneumonitis in 31% of patients (16 of 52 patients; Table 2). Increased cough and dyspnea were the most common respiratory adverse events and occurred in 15% and 12% of patients, respectively, with temsirolimus-related pneumonitis. Similar proportions of patients developed respiratory symptoms at some time on temsirolimus whether or not they developed radiographic evidence of drug-related pneumonitis (Table 3). No patient developed lung fibrosis.

Three patients who were identified as having pneumonitis based on radiographic review of chest CT images also were identified as having temsirolimus-related pneumonitis by investigators (Table 3). These patients were previously described by Bellmunt et al.[3] One patient was reported to have grade 1 pneumonitis based on CT scans but no associated respiratory symptoms or fever. No treatment for pneumonitis was given, and it resolved after 3 months with no modification to temsirolimus therapy. The second patient discontinued temsirolimus treatment as a result of disease progression and, at the same time, was diagnosed with grade 2 pneumonitis with associated fever, which progressed to grade 3. After treatment with antibiotics, the pneumonitis resolved. The third patient was diagnosed with grade 3 pneumonitis (no associated fever), for which no treatment was given. Temsirolimus treatment was delayed and then reduced and finally discontinued as a result of pneumonitis. The patient died of disease progression, possibly with pneumonitis contributing, approximately 1 month after his last dose of temsirolimus. The latter two patients had increased cough and dyspnea associated with pneumonitis. A fourth patient was identified by an investigator as having grade 2 pneumonitis with associated fever but was excluded from independent radiographic review and, therefore, from Table 3 because CT images were unreadable.

DISCUSSION

Drug-related pneumonitis is a class-effect toxicity of mTOR inhibitors.[3-7,12-18] We performed a retrospective, independent, blinded radiographic review of chest CT images of patients with previously untreated, poor-prognosis ARCC who were treated with temsirolimus or interferon to identify those with drug-related pneumonitis. This diagnosis was made based on radiographic evidence of

Table 3. Treatment-Emergent Respiratory Symptoms of Patients on Temsirolimus Who Developed Radiographically Diagnosed Drug-Related Pneumonitis Compared With Those Who Did Not

	Temsirolimus-Related Pneumonitis							
	Yes (n = 52)				No (n = 126)			
	Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3	
Adverse Event*	No. of Patients†	%	No. of Patients†	%	No. of Patients†	%	No. of Patients†	%
Any respiratory symptom	27	52	3	6	61	48	14	11
Increased cough	16	31	0	0	31	25	2	2
Dyspnea	13	25	3	6	38	30	13	10
Upper respiratory infection	4	8	0	0	10	8	0	0
Pneumonitis	3	6	1	2‡	0	0	0	0
Bronchitis	2	4	0	0	6	5	1	1
Hemoptysis	2	4	0	0	2	2	0	0
Lung hemorrhage	2	4	0	0	0		0	0
Pulmonary physical finding	2	4	0	0	7	6	0	0
Hypoxia	0	0	0	0	1	1	1	1
Respiratory failure	0	0	0	0	1	1	1	1

*Respiratory adverse events were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) and occurred at some point during temsirolimus treatment.
†A patient could have more than one adverse event.
‡An additional patient had grade 3 pneumonitis that progressed from grade 2 after discontinuation of temsirolimus treatment.

pulmonary abnormalities that developed after the initiation of treatment and could not be attributed to tumor progression or infectious complications. Analysis of 178 evaluable patients indicated that 29% developed radiographically diagnosed temsirolimus-related pneumonitis. This incidence is similar to that reported for other retrospective, independent radiographic analyses of patients treated with mTOR inhibitors. An incidence of 36% (eight of 22 patients) was reported for patients with endometrial carcinoma or neuroendocrine tumors treated with temsirolimus.[5] For the mTOR inhibitor everolimus, incidences of 39% (95 of 245 patients)[17] and 46% (13 of 28 patients)[12] were reported for patients with ARCC, an incidence of 43% (14 of 33 patients) was reported for patients with recurrent/metastatic breast cancer,[13] and an incidence of 38% (24 of 64 patients) was reported for patients with advanced non–small-cell lung cancer (NSCLC).[18]

The incidence of pneumonitis identified by investigators in the global ARCC trial was considerably less than that of pneumonitis identified by systematic radiographic analysis. Investigators identified 2% of patients as having temsirolimus-related pneumonitis,[3] whereas in this retrospective, independent, blinded review, 29% of patients were noted to have radiographic findings consistent with drug-related pneumonitis. Similarly, in a phase III study of everolimus in patients with ARCC, the incidence of pneumonitis identified by investigators was 14% and that identified by retrospective, independent, blinded review was 39%.[17] In a phase I study of the mTOR inhibitor deforolimus, 16% of patients (five of 32 patients) with advanced malignancies had interstitial and alveolar pulmonary infiltrates identified by investigators.[14] Thus, the development of radiographically detected pneumonitis is a commonly observed adverse effect of mTOR inhibitors in patients with cancer, and physicians should review chest CT images for radiographic signs of pneumonitis as part of close monitoring during treatment.

The characteristics of radiographically diagnosed pneumonitis in patients with ARCC treated with temsirolimus are similar to those of pneumonitis in other patients with cancer treated with mTOR inhibitors. For patients with ARCC, onset of pneumonitis occurred in 60% of patients within the first 8 weeks of temsirolimus treatment. For patients with endometrial carcinoma or neuroendocrine tumors treated with temsirolimus, onset of pneumonitis occurred within the first 16 weeks of treatment (median, 12 weeks; range, 12 to 16 weeks).[5] For pneumonitis that developed with everolimus treatment, median time to onset was 15 weeks in patients with ARCC,[17] 7 weeks in patients with recurrent/metastatic breast cancer,[13] and 9 weeks in patients with advanced NSCLC with no prior treatment with an inhibitor of the epidermal growth factor receptor (EGFR).[18] In all of these patients, the most common radiographic pulmonary abnormalities were ground glass opacities and parenchymal consolidation.

Radiographic changes consistent with drug-related pneumonitis as a result of mTOR inhibitors are not always associated with clinical symptoms. For temsirolimus, 31% of patients (16 of 52 patients) with ARCC and 50% of patients (four of eight patients) with endometrial carcinoma or neuroendocrine tumors who had pneumonitis, based on radiographic evidence, had respiratory symptoms around the time of onset (this study and the study by Duran et al[5]). For everolimus, 29% of patients (31 of 107 patients) and 21% of patients (22 of 107 patients) with ARCC and radiographic evidence for pneumonitis had symptoms of cough and dyspnea, respectively.[17] Similarly, 25% of patients (six of 24 patients) with advanced NSCLC who were treated with everolimus and had radiographic evidence of pneumonitis had pulmonary or respiratory symptoms.[18] These results indicate that, in the absence of symptoms, the impact of radiographically diagnosed pneumonitis on the management of patients treated with mTOR inhibitors is low.

Although 31% of patients in the global ARCC trial who were treated with temsirolimus had respiratory symptoms associated with the onset of radiographically diagnosed pneumonitis, a similar proportion of patients had respiratory symptoms at some time on treatment, whether or not radiographic review of CT images revealed pneumonitis (52% of patients with drug-related pneumonitis and 48% of patients with no drug-related pneumonitis). This similar incidence is likely a result of the baseline characteristics of

these patients.[1] As a result of having poor-prognosis ARCC, the patients had poor performance status, anemia, and a high burden of metastatic disease that often included lung metastases, all of which likely contributed to the high frequency of respiratory symptoms in this patient population.

The pulmonary abnormalities observed in patients with ARCC with temsirolimus-related pneumonitis were acute and inflammatory in nature, without evidence of long-term scarring and fibrosis. However, as more patients receive treatment with temsirolimus for longer periods of time, chronic changes indicative of some fibrotic process may occur, and physicians must be alert for these.

The pathophysiology of the pneumonitis that develops with mTOR inhibitors in patients with cancer is unclear. Suggested management recommendations are empiric and should rely on combined radiographic and clinical assessments.[3,5,13,17,19] Patients with radiographic changes indicative of pneumonitis who have no clinical symptoms may continue treatment with an mTOR inhibitor but should be monitored closely for respiratory symptoms. Patients who are receiving an mTOR inhibitor and develop symptoms with concurrent radiographic changes should have treatment held during further evaluation and management, which may include diagnostic tests such as pulmonary function tests and bronchoscopy, as well as initiation of empiric treatments such as corticosteroids and antibiotics. Treatment with the mTOR inhibitor might be resumed, with or without dose reduction, depending on the patient's clinical course, response to empiric therapies, availability of other treatment options, and overall risk/benefit assessment.

Pneumonitis that occurs with an mTOR inhibitor is different from that occurring with the targeted inhibitors of EGFR.[20] Approximately 1% of patients treated with the EGFR inhibitor gefitinib developed interstitial lung disease (2% of Japanese patients).[21,22] Dyspnea, with or without a cough, or low-grade fever often was associated with onset. Approximately one third of gefitinib-associated pneumonitis was fatal.

Our report highlights the high incidence of radiographically detected pneumonitis in patients with cancer treated with mTOR inhibitors, which may not be recognized by physicians. Attention must be paid to patients with pulmonary abnormalities identified by radiographic review of chest CT images. If pneumonitis related to mTOR inhibitors is diagnosed, patients should be monitored closely, and their management should be altered if clinical symptoms develop. Further studies are needed to define the mechanism of mTOR inhibitor–related pneumonitis and the role of pulmonary function testing and other evaluations in the management of patients with cancer treated with mTOR inhibitors. Although pneumonitis has been associated with mTOR inhibitors that are derivatives of sirolimus, it is not clear whether newer agents that inhibit mTOR by other mechanisms (eg, mTOR kinase inhibitors or PI3K or AKT inhibitors[23,24]) are associated with this adverse effect. Vigilance in the clinical trials of these new agents is necessary to determine whether radiographically detected pneumonitis occurs during treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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