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Drug-related pneumonitis during mTOR inhibitor therapy in patients with neuroendocrine tumors: A radiographic pattern-based approach

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Abstract

Purpose—Investigate the incidence of drug-related pneumonitis during mTOR inhibitor therapy in patients with neuroendocrine tumors (NET), and characterize radiographic patterns of pneumonitis.

Methods—Sixty-six patients (39 males, 27 females, age: 22-79 years) with advanced NET treated with mTOR inhibitor, everolimus, were retrospectively studied. Chest CT scans during therapy were reviewed for abnormalities suspicious for drug-related pneumonitis by an independent review of two radiologists. Extent, distributions, and specific findings were evaluated in cases positive for pneumonitis. Radiographic patterns of pneumonitis were classified using ATS/ERS classification of interstitial pneumonia.

Results—Drug-related pneumonitis was radiographically detected in 14 patients (21%). Time from the initiation of therapy to pneumonitis was within 6 months of therapy in 10 patients (71%), while it ranged from 1.0 to 27.7 months. Pneumonitis was more common in patients who had never smoked ($p=0.03$). Lower lungs were more extensively involved than upper and middle lungs. Peripheral and lower distribution was most common ($n=8$), followed by peripheral and multifocal distribution ($n=3$). Ground glass and reticular opacities were present in all cases, with consolidation in 8 cases. The radiographic pattern of pneumonitis was classified as cryptogenic

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Conflict of Interest

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organizing pneumonia (COP) pattern in 8, non-specific interstitial pneumonia (NSIP) pattern in 5, and hypersensitivity pneumonitis (HP) pattern in one patient.

Conclusion—Drug-related pneumonitis was noted in 21% of the advanced NET patients treated with everolimus. Radiographic pattern of pneumonitis was most commonly COP pattern, followed by NSIP pattern.

Keywords

mTOR inhibitor; pneumonitis; drug toxicity; computed tomography; neuroendocrine tumors

INTRODUCTION

Drug-related pneumonitis is one of the major categories of drug toxicity during anti-cancer systemic therapy, and demonstrates a spectrum of radiographic manifestations on chest computed tomography (CT)^{1, 2}. It is also known that the lung's response to injury is limited and can be classified into several common types of histologic manifestations with corresponding radiographic patterns¹, thus allowing for description according to the classification of interstitial pneumonias and related lung diseases^{2, 3}. With the recent rapid advances of precision medicine for cancer and the accelerated clinical application of novel anti-cancer agents in clinical oncology, the role of imaging in detecting and monitoring therapy-specific toxicities is becoming increasingly important²⁻⁴. A prior study from our group has introduced the radiographic pattern based approach to characterize pneumonitis during mTOR (mammalian target of rapamycin) inhibitor therapy according to American Thoracic Society(ATS)/European Respiratory Society (ERS) classification of interstitial pneumonias, in a cohort of Waldenström macroglobulinemia as a paradigm^{2, 5, 6}. The study demonstrated a high incidence of mTOR pneumonitis (58%), radiographically manifesting cryptogenic organizing pneumonia (COP) pattern or non-specific interstitial pneumonia (NSIP) pattern². The same approach was also used to characterize immune-related pneumonitis during anti-PD-1 therapy among melanoma patients³, indicating the applicability of the approach for different cohorts of cancer patients under specific therapy.

The mammalian target of rapamycin (mTOR) is a well-studied oncogenic driver in human cancers, and involves the critical junctures of PI3K/Akt/mTOR pathway⁷. Everolimus is a rapamycin analogue and selectively inhibits mTOR, and has been approved for treatment of renal cell carcinomas (RCC), advanced neuroendocrine tumors (NET) of the pancreas, subependymal giant cell astrocytoma in tuberous sclerosis, and advanced hormone receptor-positive, HER2-negative breast cancer⁷⁻⁹. Drug-related pneumonitis is a well-known class-effect toxicity of everolimus and other mTOR inhibitors¹⁰, and has been studied in several prior studies of advanced RCC patients with the reported incidence of pneumonitis of 23-30% among everolimus-treated patients¹¹⁻¹³. In a trial of everolimus in advanced non-small-cell lung cancer (NSCLC), drug-related pneumonitis was noted radiographically in 25% of the cohort¹⁴. Among the cohorts of advanced NET, drug-related pneumonitis was noted in 12% of the patients treated with everolimus in a phase 3 trial¹⁵, and in 8% of the patients treated with everolimus plus octreotide long-acting repeatable in another phase 3 trial¹⁶. While these clinical studies reported drug-related pneumonitis as an important class effect of mTOR inhibitor therapy among NET patients, detailed descriptions of the

radiographic patterns of pneumonitis according to ATS/ERS classifications have not been previously reported. Likewise, a few sporadic clinical case reports described pneumonitis during everolimus therapy for NET^{17, 18}, without using systematic approach to characterize its radiographic pattern.

The objectives of the study are to determine the incidence of drug-related pneumonitis detected on chest CT scans among patients with advanced NET treated with mTOR inhibitor, everolimus, and characterize radiographic patterns of pneumonitis according to ATS/ERS classifications of interstitial pneumonias.

MATERIALS AND METHODS

Patients and CT scans

The study population included 66 patients with advanced NET treated with mTOR inhibitor therapy using everolimus at the Dana-Farber Cancer Institute, who had baseline and at least one follow-up chest CT during therapy available for review. Patients were identified through the query of the institutional review board (IRB)-approved CRIS (clinical research information system) database of NET patients. All patients provided written informed consent upon enrollment to CRIS.

Patients underwent baseline chest CT scans prior to the initiation of everolimus therapy (median time from baseline CT to therapy initiation: 1.6 weeks). All chest CT scans after therapy initiation until the termination of therapy or the last follow-up (for those who are still on therapy) were included as follow-up scans. Patients treated on trials (n=52) had follow-up CT scans at the intervals as defined in the trial protocols (every 8 weeks in 41; every 12 weeks in 11 patients). For patients treated clinically without being enrolled to trials (n=14), follow-up CT scans were performed per treating clinical providers' discretion without predefined intervals. The median time between therapy initiation and the first follow-up CT was 8.0 weeks.

The standard clinical chest CT protocol utilized a 64-row MDCT scanner (Aquilion 64; Toshiba America Medical Systems, CA). Iodinated intravenous contrast agent was used unless medically contraindicated. Patients were scanned at end-inspiration in the supine position from the cranial to caudal direction from the clavicles to the adrenal glands. Axial images with 5 mm thickness were reconstructed using standard and lung algorithms. Axial images reconstructed with the lung algorithm were reviewed on Picture Archiving Communication Systems workstations (Centricity, GE Healthcare), as described previously².

Chest CT review during mTOR inhibitor therapy

Baseline chest CT and follow-up chest CT scans performed during mTOR inhibitor therapy were retrospectively reviewed with the IRB approval. All chest CT scans were evaluated for abnormalities suspicious for drug-related pneumonitis by an independent review of two board-certified radiologists with expertise in thoracic imaging (M.N., H.H.). The radiologists were aware that the patients had advanced NET and received everolimus therapy, however, did not have access to the detailed clinical data including adverse events

and tumor progression. Each set of baseline and follow-up chest CT scans belonging to a patient were reviewed sequentially in one session, and radiologists were aware of the scan dates².

Chest CT images were evaluated for the presence of parenchymal and interstitial lung abnormalities suspicious for drug-related pneumonitis². On the basis of the review of sequential CT scans, each radiologist independently recorded whether radiographic drug-related pneumonitis is present in each case, using a five-point scale: 1=definitively not, 2=probably not, 3=equivocal, 4=probably, and 5=definitively^{2, 3}. Patients with scores 4 or 5 were considered to be positive for pneumonitis^{2, 3}. Radiologists were instructed to disregard the findings indicative of tumoral involvement of the lung^{2, 19}. Discrepancies between two readers were resolved by a consensus review of the original two readers (M.N., H.H.) and an additional radiologist (N.R.).

For cases that were positive for pneumonitis, the abnormalities indicative of drug-related pneumonitis were further evaluated for 1) extent in terms of upper, middle and lower lungs using a 5-point scale (0: no involvement, 1: <5%, 2: 5%-25%, 3: 25%-50%; 4: >50%); 2) distribution in terms of peripheral, diffuse, central, or mixed; 3) distribution in terms of upper predominant, lower predominant, diffuse, multifocal, or focal; and 4) lobar involvement^{2, 3}. The presence or absence of specific CT findings including ground glass opacities (GGO), reticular opacities, consolidation, centrilobular nodularity, traction bronchiectasis, and honeycombing was recorded^{2, 3}. In each case, radiographic patterns of pneumonitis were classified referring to ATS/ERS international multidisciplinary classification of interstitial pneumonias and the related conditions^{5, 6} as 1) usual interstitial pneumonia (UIP) pattern, 2) non-specific interstitial pneumonia (NSIP) pattern, 3) cryptogenic organizing pneumonia (COP) pattern, 4) acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern, 5) hypersensitivity pneumonitis (HP) pattern, and 6) not applicable, as previously described^{2, 3}.

Medical records of the cases positive for pneumonitis were reviewed for the respiratory symptoms at the time of radiographic pneumonitis.

Statistical analysis

Demographics and clinical characteristics between patients with and without drug-related pneumonitis were compared using Fisher exact test for categorical data and Wilcoxon test for continuous data. Kaplan-Meier method was used to obtain the median time to the onset of drug-related pneumonitis. All *p* values were based on a two-sided hypothesis. A *p* value of less than 0.05 was considered to be significant.

RESULTS

Table 1 summarizes the demographics and baseline disease characteristics of 66 patients. Radiographically-detected drug-related pneumonitis was noted in 14 patients (21%). Time from the initiation of everolimus therapy to the diagnosis of pneumonitis ranged from 1.0 to 27.7 months, with the estimate of 25th percentile (25% of the patients having pneumonitis)

of 16.0 months (Fig. 1). In 10 of the 14 patients (71%), radiographic pneumonitis was noted within 6 months of therapy.

Never smoker status was significantly more common in the pneumonitis group (12/14, 86%) compared to the non-pneumonitis group (27/52; 52%) ($p=0.03$). No other clinical characteristics appeared to be associated with pneumonitis. No difference was noted in the incidence of pneumonitis among patients treated with single-agent everolimus therapy and those treated with combination therapy using everolimus and other agents ($p=0.1$). Among 11 patients with pneumonitis during combination therapy, 7 received octreotide, 2 received octreotide plus temozolomide, one received temozolomide, and one received pasireotide, along with everolimus. Time on mTOR inhibitor therapy did not differ between patients with and without pneumonitis (median time on therapy: 19.4 and 16.3 months, respectively; log-rank $p=0.60$).

Table 2 summarizes the details of CT characteristics of the 14 patients with drug-related pneumonitis. The extent of involvement was higher in lower lungs than upper and middle lungs. Bilateral lungs were involved in all but one patient. Distribution of the CT findings was most commonly peripheral and lower ($n=8$), followed by peripheral and multifocal ($n=3$). Diffuse involvement was seen in 2 patients, and one patient had mixed (in terms of central vs. peripheral) and lower distribution. Among the specific CT findings, GGO and reticular opacities were present in all 14 patients, along with consolidation in 8 patients. Centrilobular nodularity, traction bronchiectasis, or honeycombing was not noted in any of the cases. The overall radiographic pattern of pneumonitis on chest CT was most commonly COP pattern ($n=8$), followed by NSIP pattern ($n=5$) (Figs. 2, 3, respectively). Hypersensitivity pneumonitis pattern was noted in one patient (Fig. 4). Patient characteristics were not different among patients with different pneumonitis patterns.

Six of the 14 patients (43%) had respiratory symptoms at the time of radiographic pneumonitis, including shortness of breath ($n=2$), cough ($n=2$), mild hoarseness ($n=1$), and sore throat ($n=1$). The remaining 8 patients were asymptomatic. Everolimus was continued in 6, discontinued in 5, and temporarily held and restarted later in 3 patients. Two patients with shortness of breath were treated with prednisone, including one who was admitted for treatment and restarted everolimus later, and the other treated as outpatient and discontinued everolimus.

DISCUSSION

Radiographic pneumonitis was identified in 21% of the advanced NET tumor patients treated with everolimus therapy. Never smoker and islet cell tumor histology were associated with pneumonitis. The CT findings of pneumonitis were more extensive in lower lungs, and had predominantly peripheral and lower distribution. The most common radiographic pattern of pneumonitis was COP pattern, followed by NSIP pattern. The study provided the radiographic details of pneumonitis during mTOR inhibitor therapy in patients with advanced NET, and defined the radiographic patterns of pneumonitis using ATS/ERS classification.

Radiographic pneumonitis was present in 21% (14/66) of the patients in the present cohort. The incidence is somewhat higher compared to the prior trials of everolimus in advanced NET patients. A phase 3 study of everolimus for advanced pancreatic NET reported drug-related pneumonitis in 25 of the 204 patients (12%) treated with everolimus, including 5 patients (2%) with grade 3 or 4 events¹⁵. In a phase 3 trial of plus octreotide long-acting repeatable for advanced NET associated with carcinoid syndrome (RADIANT-2), 8% (18/215) of the patients who received everolimus plus octreotide developed pneumonitis¹⁶. It is possible that the mildest spectrum of radiographic pneumonitis without clinical symptoms is not fully captured in these clinical studies. Indeed, both studies described higher incidence of pneumonitis (17% in the study by Yao et al, and 12% in RADIANT-2), when a wider spectrum of pulmonary findings such as “interstitial lung disease”, “lung infiltration”, and “pulmonary fibrosis” were included^{15, 16}. Some of these findings may represent radiographic pneumonitis with COP or NSIP pattern detected in the present study. Additionally, a more recent study of 169 neuroendocrine tumor patients in a compassionate use program reported pneumonitis of any grade in 18.9% of the patients, and grade 3-4 pneumonitis in 8.3%²⁰, which is comparable to the present results given that the present study focused on radiographically detected pneumonitis and did not require clinical symptoms for diagnosis.

The incidence of pneumonitis in the present study is slightly lower when compared with the prior studies of mTOR pneumonitis in other solid tumors, including 36% in metastatic RCC patients treated with everolimus or temsirolimus¹², 29% in advanced RCC patients treated with temsirolimus¹³, and 25% among advanced NSCLC patients who received everolimus¹⁴. The incidence in the present study is less than half of the incidence in the prior study in Waldenström macroglobulinemia, in which 58% of the patients had radiographic pneumonitis². It is possible that patients with different tumor types may have different susceptibility to develop mTOR pneumonitis, which needs to be further investigated in a larger cohort of patients treated with the same regimen, in order to account for other variables that can confound the observation.

In the majority of the cases (10/14; 71%), time from therapy start to radiographic pneumonitis was within 6 months, while a wide range (1.0-27.7 months) was noted with the estimate of 25th percentile was 16 months. Although the limited data are available in the previous reports for the timing of pneumonitis during mTOR inhibitor therapy, the time interval to pneumonitis after therapy initiation in the present study appears to be somewhat longer and has wider range compared to the prior reports. In a study by Duran et al of 22 patients with advanced NET (n=15) or endometrial carcinoma (n=7), all cases of pneumonitis were noted within the first 16 weeks after treatment start, with a median of 12 weeks (range: 2-16 weeks)²¹. In another study of 178 advanced RCC patients treated with temsirolimus, 60% of pneumonitis developed within 8 weeks of therapy¹³. While the exact mechanism of the differences is unclear, the result of the present study indicates the need for close monitoring of lung abnormalities on CT throughout the course of mTOR inhibitor therapy.

Notably, pneumonitis was more common in never smokers in this study, which is somewhat contrary to the general concept of lung injury, which assumes that smokers' lungs are more

prone to injury²². A prior study by Duran et al also reported a similar finding, where 6 out of 8 mTOR pneumonitis patients were non-smokers²¹. The observation needs to be carefully examined for confounders and reproducibility in larger cohorts.

The incidence of pneumonitis did not differ between the everolimus single-agent group and the combination therapy group, as in the prior study in Waldenstrom macroglobulinemia². Among the combination agents used in the pneumonitis group, the most common agent was octreotide, which is not recognized as a major pulmonary-toxic agent. Temozolomide, which was given in 3 patients in the pneumonitis group, is known to cause pneumonitis²³⁻²⁶, and it is not possible to exclude its added effect. However, no significant association was noted between pneumonitis and temozolomide use among 60 patients treated with combination therapy ($p=0.73$).

The detailed assessment of the CT characteristics of pneumonitis demonstrated a higher extent of involvement in lower lobes, with predominantly peripheral and lower distribution, which closely simulates the findings in the prior study of mTOR pneumonitis in Waldenstrom macroglobulinemia². Presence of GGO and reticular opacities in all cases, with consolidation in some cases, are also consistent with the specific CT findings in the prior studies in NET and other tumors^{2, 12, 21}. Radiographic pattern of pneumonitis according to ATS/ERS classification was most frequently COP, followed by NSIP, as in the Waldenstrom macroglobulinemia cohort². The results further support the concept of pneumonitis as a “class-effect” of mTOR inhibitors, which induces similar lung injury patterns across different cohorts and tumor types. One patient had a radiographic pattern of hypersensitivity pneumonitis, which was not noted in the prior cohort². Hypersensitivity pneumonitis could be a relatively uncommon manifestation in the spectrum of mTOR pneumonitis, which needs further investigation.

Respiratory symptoms were noted in 43% (6/14) of the patients at the time of pneumonitis in our cohort, which is consistent with the prior reports describing a lack of clinical symptoms in 50% or more cases of radiographic mTOR pneumonitis. Among 8 patients with mTOR pneumonitis reported by Duran et al, a half of the patients were asymptomatic, and the remaining half most commonly had cough or dyspnea²¹, as noted in our cases. In a prior study by Maroto et al, only 31% (16/52) of the patients had respiratory symptoms, indicating that mTOR pneumonitis may not be detected based on clinical assessment alone¹³.

The limitations of the present study include a retrospective design and a small number of patients treated at a single institution. Tumor histology and primary sites of NET varied among the patients in this cohort. Not all patients were treated with single-agent everolimus, which is certainly a limitation as discussed in detail. A small size of the present cohort did not allow further investigation of the association between never smokers and pneumonitis, due to the lack of statistical power and the risk of overfitting in multivariable logistic regression models. The association between tumor response and pneumonitis is another topic of interest and remains to be investigated in a larger cohort with a sufficient number of patients at an optimal landmark timepoint. The diagnosis of drug-related pneumonitis was based on CT findings; however, similar approaches have been utilized in the prior publications by our group and others^{2-4, 13, 21}. Pneumonitis was not confirmed by histology,

which is often the case with patients with known advanced malignancy receiving systemic therapy.

In conclusion, radiographic pneumonitis during everolimus therapy was noted in 21% patients with advanced NET, and most commonly demonstrated bilateral ground glass and reticular opacities, with or without consolidation, in peripheral and lower distribution. Overall radiographic pattern was indicative of COP or NSIP pattern. Similarities of the radiographic pattern of pneumonitis across the studies of mTOR pneumonitis in different cohorts support the class-effect concept of mTOR-related lung toxicity, and indicate the utility of a systematic approach proposed in the present study for further investigation of this important adverse event.

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Highlights

- mTOR pneumonitis was noted in 21% of advanced NET patients treated with everolimus
- Pneumonitis was more common in patients who had never smoked
- Pneumonitis most commonly presented COP pattern, followed by NSIP pattern on CT
- Radiographic pattern based approach is useful to study this class effect of mTOR

Fig 1.
Cumulative probability of radiographic drug-related pneumonitis in advanced neuroendocrine tumor patients during mTOR inhibitor therapy.

Fig 2.

A 74 year-old male with advanced neuroendocrine tumor of the lung origin treated with single-agent everolimus therapy.

Chest CT scan at 1 months of therapy demonstrated new bilateral GGO, reticular opacities, and consolidation (arrows) in peripheral and lower distribution, representing cryptogenic organizing pneumonia (COP) pattern. The patient was symptomatic with shortness of breath and hypoxia, and was treated with predonisone for mTOR pneumonitis.

Fig 3.

A 65 year-old male with advanced pancreatic neuroendocrine tumor treated with everolimus along with temozolomide and octreotide.

Chest CT scan at 1.6 months of therapy demonstrated GGO and reticular opacities in peripheral and lower distribution in bilateral lower lobes (arrows), indicative of non-specific interstitial pneumonia (NSIP) pattern.

Fig 4.

A 62 year-old female with advanced pancreatic neuroendocrine tumor treated with everolimus and temozolomide.

A, B. Chest CT scan at 10.3 month of therapy showed diffuse bilateral GGO and reticular opacities involving all lobes, noted as diffuse increase of lung attenuation on CT, demonstrating hypersensitivity pneumonitis (HP) pattern. The patient was symptomatic with mild shortness of breath, and was treated with predonisone for mTOR pneumonitis.

Table 1
Patient demographics and clinical characteristics

Characteristics		With Pneumonitis (n=14)	Without Pneumonitis (n=52)	Total (n=66)	P value
Sex	Male	9	30	39	0.76
	Female	5	22	27	
Median age (years)		60	55	55.4	0.21
Race	White	11	50	61	0.06
	Black	1	1	2	
	Asian	1	0	1	
	Unknown	1	1	2	
Smoking	Current/former	2	25	27	0.03*
	Never	12	27	39	
Primary site	Pancreas	8	30	38	0.16
	Small bowel	1	13	14	
	Lung	2	6	8	
	Rectum	1	0	1	
	Unknown	2	3	5	
Tumor differentiation	Well-differentiated	12	47	59	0.56
	Poorly-differentiated	1	1	2	
	Unknown	1	4	5	
Single-agent vs. combination	Single-agent	3	3	6	0.10
	Combination therapy	11	49	60	
Prior therapy ^{\$}	Cytotoxic	8	29	37	1.00
	Octoreotide	12	37	49	0.33
	TKI [^]	3	11	14	1.00
	Interferon	1	5	6	1.00

^{\$} Prior therapy: The number of patients who received the therapy prior to initiating mTOR inhibitor are listed.

[^] TKI: tyrosine kinase inhibitor

Table 2
Imaging characteristics of pneumonitis in 14 patients

Extent					
	None	<5%	5-25%	25-50%	>50%
Upper lung	2	4	6	1	1
Middle lung	0	5	6	2	1
Lower lung	1	0	3	7	3
Distribution 1					
Upper	Lower	Diffuse		Multifocal	Focal
0	9	2		3	0
Distribution 2					
Peripheral	Diffuse		Central		Mixed
11	2		0		1
Lobar involvement: Number of lobes involved					
One	Two	Three	Four	Five	Six (All lobes)
1	3	2	2	1	5
Lobar involvement: For each lobe					
RUL	RML	RLL	LUL	Lingula	LLL
6	10	13	6	8	13