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Original Research

Drug-related pneumonitis during mammalian target of rapamycin inhibitor therapy in patients with neuroendocrine tumors: a radiographic pattern-based approach

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Abstract ***Purpose:*** The purpose of this study was to investigate the incidence of drug-related pneumonitis during mammalian target of rapamycin (mTOR) inhibitor therapy in patients with neuroendocrine tumours (NET) and characterise 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 computed tomography 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 the American Thoracic Society/European Respiratory Society 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 distributions were most common ($n = 8$), followed by peripheral and multifocal distributions ($n = 3$). Ground glass and reticular opacities were present in all cases, with consolidation in eight cases. The radiographic pattern of pneumonitis

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was classified as cryptogenic organising pneumonia (COP) pattern in eight patients, non-specific interstitial pneumonia (NSIP) pattern in five, and hypersensitivity pneumonitis 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.

1. 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 patterns [1], 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 important [2–4]. A prior study from our group has introduced the radiographic pattern-based approach to characterise pneumonitis during mammalian target of rapamycin (mTOR) inhibitor therapy according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) classification of interstitial pneumonias, in a cohort of Waldenstrom's macroglobulinemia as a paradigm [2,5,6]. The study demonstrated a high incidence of mTOR pneumonitis (58%), radiographically manifesting cryptogenic organising pneumonia (COP) pattern or non-specific interstitial pneumonia (NSIP) pattern [2]. The same approach was also used to characterise immune-related pneumonitis during anti-PD-1 therapy among melanoma patients [3], indicating the applicability of the approach for different cohorts of cancer patients under specific therapy.

The mTOR is a well-studied oncogenic driver in human cancers and involves the critical junctures of phosphoinositide 3-kinase/Akt/mTOR pathway [7]. Everolimus is a rapamycin analogue and selectively inhibits mTOR and has been approved for treatment of renal cell carcinomas (RCC), advanced neuroendocrine tumours (NET) of the pancreas, subependymal giant cell astrocytoma in tuberous sclerosis, and advanced hormone receptor-positive, HER2-negative breast cancer [7–9]. Drug-related pneumonitis is a well-known class–effect toxicity of everolimus and other mTOR inhibitors [10] and has been studied in several prior studies of advanced RCC patients with the reported incidence of pneumonitis of 23–30% among everolimus-treated patients [11–13]. In a trial of everolimus in advanced non-small-cell lung cancer (NSCLC), drug-related pneumonitis was noted radiographically in 25% of the cohort [14]. Among the cohorts of advanced NET, drug-related pneumonitis was noted in 12% of the patients treated with everolimus in a phase III trial [15] and in 8% of the patients treated with everolimus plus octreotide long-acting repeatable in another phase III trial [16]. 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 characterise 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 characterise radiographic patterns of pneumonitis according to ATS/ERS classifications of interstitial pneumonias.

2. Materials and methods

2.1. 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 clinical research information system (CRIS) database of NET patients. All patients provided written informed consent upon enrolment 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