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Case Report and Literature Review

Everolimus induced Pneumonitis

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Abstract

Everolimus (RAD 001) is an orally administered inhibitor of mTOR (mammalian target of rapamycin), a central regulator of intracellular signaling pathways involved in cell growth and proliferation, cellular metabolism and angiogenesis. Drug is currently in use to prevent allograft rejection after solid organ transplantation and in treatment of advanced renal cell carcinoma (RCC). Noninfectious pneumonitis is rare adverse reaction associated with rapamycin and rapamycin analogues. Awareness of this toxicity and

appropriate management is important to optimize patient safety. Here we report a case of everolimus induced pneumonitis in a 72 years old male with metastatic renal cell carcinoma (mRCC) after 4 months of commencement of everolimus. Drug was discontinued and patient was treated accordingly and discharged after 10 days of hospital admission.

Keywords

Everolimus, Rad 001, Pneumonitis, Advanced Renal Cell Carcinoma, Metastatic Renal Cell Carcinoma (mRCC)

Introduction

Everolimus is an orally administered inhibitor of mammalian target of rapamycin (mTOR) and was approved by US Food & Drug Administration (US FDA) in March 2009 and by European Medicines Agency (EMA) in Aug 2009 for the treatment of un resectable or metastatic RCC(1). mTOR is a cytoplasmic Serine/threonine kinase that acts as an integration point for three key inputs (i) extracellular stimulation by growth factors including vascular endothelial growth factor (VEGF) (ii) nutrient availability and (iii) intracellular energy status^(2–5). Everolimus demonstrated prolonged progression free survival in RECORD – 1 (renal cell cancer treatment with oral RAD 001 given daily) the pivotal Phase III, randomized, placebo–controlled trial of patients with mRCC who have progressed on VEGF receptor tyrosine kinase inhibitor therapy(6). Non–infectious pneumonitis is a non–dose dependent adverse reaction associated with rapamycin and rapamycin analogues. Pulmonary toxicity has been reported in up to 11% of patients receiving sirolimus⁽⁷⁾ and in 1–36 % receiving temsirolimus(8–9). Prospective analysis of thoracic radiographic assessment performed every 8–week in 274 patients receiving Everolimus who were enrolled in RECORD – 1, phase III trial was

carried out by blinded central review(10),interstitial pneumonitis was suspected in 13.5 % of patients, but only 3.6 % of them have grade 3 events (those interfering with daily living or with oxygen required). Here we report a case of 72 years male with mRCC, who developed non–infectious pneumonitis after 4 months of starting everolimus. Sign, symptoms and radiographic findings in this case report were almost similar to the findings described in patients who developed pneumonitis in RECORD–1 trial.

Case Report

A 72 years old male was diagnosed with metastatic renal cell carcinoma (clear cell type) at presentation (lung metastases). He was started on sunitinib (tyrosine kinase inhibitor) and remained on sunitinib for 2 months. He underwent cytoreductive left nephrectomy and after that he was continued on sunitinib for more 2 months. He was switched to sorafenib due to progressive metastatic disease in

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Grade	Intervention	Investigations	Everolimus Dose Adjustment
<p>Grade 1 Asymptomatic, radiographic findings only</p>	<ul style="list-style-type: none"> • If asymptomatic, follow up with careful clinical assessment at each visit • Those with baseline radiographic findings should have close interval assessment with chest CT and/or be managed as having grade 2 toxicity 	<ul style="list-style-type: none"> • Routine radiographic follow-up if asymptomatic 	<ul style="list-style-type: none"> • Continued without dose adjustment
<p>Grade 2 Symptomatic, not interfering with activities of daily living</p>	<ul style="list-style-type: none"> • Corticosteroids may be helpful for troublesome symptoms if dose alteration is not effective 	<ul style="list-style-type: none"> • Diagnostic or therapeutic measures to exclude an infectious origin or other causes of radiographic infiltrates/respiratory symptoms such as fluid overload or pulmonary embolus, should be performed, preferably before starting corticosteroids 	<ul style="list-style-type: none"> • Temporary interruption or a decrease in dose to 5 mg daily with close observation for resolution of symptoms • With improvement to an asymptomatic status, everolimus may be reintroduced, if interrupted, at a reduced dose of 5 mg daily with close observation • If no recovery to grade \leq 1 discontinue everolimus
<p>Grade 3 Symptomatic, interfering with activities of daily living, oxygen indicated</p>	<ul style="list-style-type: none"> • Corticosteroids may be indicated until clinical symptoms resolve • High dose methylprednisolone in patients with respiratory distress • Lower doses of corticosteroids may be used in less severe cases • In general, for any patient with significant respiratory compromise, corticosteroids should be given urgently while the evaluation is proceeding 	<ul style="list-style-type: none"> • Bronchoscopy and other diagnostic tests as indicated, be done to exclude any infectious etiology, particularly given the risk of opportunistic infection with the mTOR inhibitors • Other causes such as pulmonary emboli or progressive metastatic disease should also be considered 	<ul style="list-style-type: none"> • Should be discontinued • With resolution of evidence of toxicity, may be reinitiated at a reduced dose of 5 mg daily in select clinical circumstances with proven advantage and close follow-up
<p>Grade 4 Life-threatening, Ventilation support indicated</p>	<ul style="list-style-type: none"> • Corticosteroids should be given 	<ul style="list-style-type: none"> • Exclude other possible etiologies 	<ul style="list-style-type: none"> • Should be permanently discontinued • Should not be reinstated even with resolution of pneumonitis

Table 1 : Management of Noninfectious Pneumonitis: Treatment Recommendations ^{1,21}



Figure 1a : Pre Everolimus CT chest



Figure1b : Pre Everolimus CT chest



Figure 2 : Post Everolimus chest X–ray showing bilateral interstitial edema with infiltrates in right lower lung zone

lung. He remained on sorafenib for 8 months with good response in initial 4 months. He was started on everolimus 10 mg daily, because of progressive disease. There was an overall good response to everolimus. After 4 months of initiation of everolimus, patient presented with the complaints of cough

and dyspnea for 15 days and fever for 5 days. On physical examination, poor general condition is noted with temperature of 38°C, tachycardia and bilateral crepitation. Laboratory findings were: arterial blood gas: pH 7.40, pCO₂ 29 mmHg, pO₂ 57 mmHg, HCO₃ 20 mmol/l, O₂ saturation of 90 % (picture of compensated respiratory alkalosis), 5800 WBC/cmm, hemoglobin 9.8 g/dl, platelets 270,000/cmm, serum creatinine 2.2 mg/dl, plasma HCO₃ 20 mmol/l. His baseline chest CT (Fig. 1a, 1b) was negative for any sign of pneumonitis. On chest X–ray (Fig. 2) bilateral interstitial edema with infiltrates in right lower lung zones was seen and chest CT (Fig. 3a, 3b) showed diffuse ground glass opacity in bilateral upper and lower lobes especially in apical and basal segment of lower lobes along with loculated pleural effusion in major fissure on right side with small septal thickening. Blood cultures and sputum cultures were negative for any organism. There was no evidence of left heart failure by echocardiography. Bronchoalveolar lavage (BAL) with fiberoptic bronchoscopy was performed, and analysis of the BALF cells showed 1.49×10⁵ cells/mL; macrophages (44.3%), lymphocytes (42.9%), neutrophils (12.3%), eosinophils (0.5%). Microbiological evaluation of the BALF revealed negative results for bacteria and fungi. The drug lymphocyte stimulation test (DLST) for everolimus was negative (stimulation index 40%). Everolimus was discontinued from the day of admission. Patient was initially treated with empiric wide spectrum antibiotics and supplemental O₂ with no clinical improvement. After 3 days, steroids were introduced suspecting everolimus induced pneumonitis. 100 mg I/V methylprednisone three times per day were started with tapering doses over time. Patient's clinical and radiological condition was improved within 2 days of starting steroids with decreased need of supplemental O₂. Chest X–ray (Fig. 4) at 6th day of admission showed few residual infiltrates on right side with complete resolution of bilateral interstitial edema. Arterial blood gases also showed improvement with pH of 7.4, pCO₂ 36 mmHg, pO₂ 96 mmHg, HCO₃ 24mmol/l, O₂ saturation 97 % and serum creatinine of 1.5 mg/dl. Patient was discharged after 10 days without any need of supplemental O₂ at home and on tapering doses of steroids with discontinuation of everolimus.

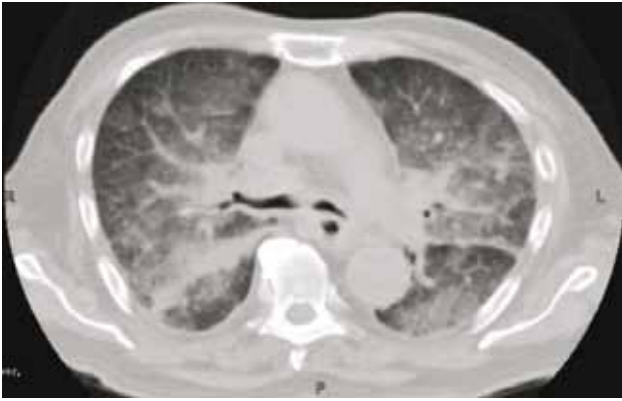


Figure 3a : Post Everolimus CT chest showing diffuse ground glass opacity

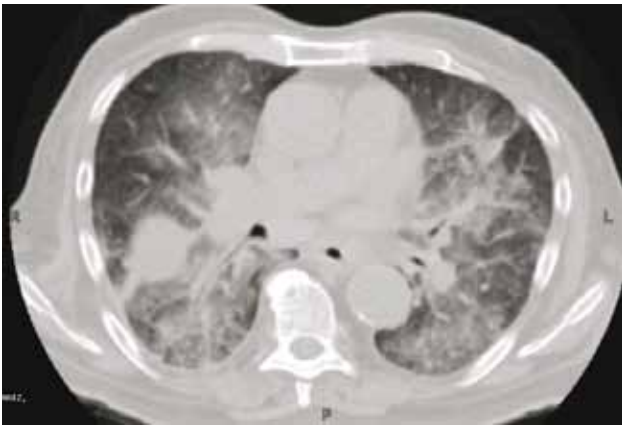


Figure 3b : Post Everolimus CT chest showing loculated pleural effusion in major fissure on right side with small septal thickening along with diffuse ground glass opacity



Figure 4 : CT chest showing few residual infiltrates on right side with complete resolution of bilateral interstitial edema after discontinuation of Everolimus

Discussion

Everolimus (RAD 001) is an orally administered selective inhibitor of mammalian target of rapamycin (mTOR) with a molecular structure very similar to that of sirolimus⁽¹¹⁾. The action of everolimus with

in mammalian target of rapamycin (mTOR) pathway results in decreased protein synthesis, decreased angiogenesis and cycle arrest⁽¹²⁾. Currently, drug is in use to prevent allograft rejection after solid organ transplantation⁽¹³⁾ and in treatment of advanced renal cell carcinoma⁽⁶⁾. The RECORD –1 (renal cell carcinoma treatment with oral RAD 001 given daily) the pivotal phase III randomized placebo–controlled trial assessed everolimus in patients with mRCC, who progressed on vascular endothelial growth factor receptor – tyrosine kinase inhibitor (VEGFr–TKI) therapy had showed prolonged progression free survival^(6,14). It can be considered as a suitable treatment option for patients with VEGFr – TKI refractory disease. A usual starting dose for patients with renal cell carcinoma is 10mg daily⁽¹²⁾. According to systematic review, most commonly reported adverse events associated with everolimus include anemia, hyperglycemia, hypercholesterolemia, mucositis, fatigue and rash⁽¹²⁾. Noninfectious pneumonitis is a rare adverse event associated with rapamycin and rapamycin analogues⁽⁹⁾ and its characterized by noninfectious nonmalignant infiltrates⁽¹⁰⁾, possibly representing a hypersensitivity reaction; however, its etiology has not been fully characterized^(7, 15). These drugs have been associated with a 5–15% incidence of pneumonitis after solid organ transplant with a wide spectrum of disease severity, varying from subclinical to fulminant^(7, 16–18). Pneumonitis includes interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar hemorrhage, alveolitis and pulmonary toxicity⁽¹⁴⁾. The pathogenic mechanism of everolimus–associated pulmonary toxicity is not well understood. Both a direct, dose dependent toxicity and an autoimmune response or delayed hypersensitivity reaction triggered by exposure to rapamycin analogues with or without a cryptic pulmonary antigen have been considered as possible underlying pathogenic mechanisms^(7, 19). Radiographic findings are usually consistent with ground glass attenuation and patchy consolidation^(8, 15, 19, 20), but may be misleading and misinterpreted as progressive pulmonary disease with new nodular metastatic lesion, which is an important problem of therapy associated pneumonitis. So in patients with mTOR inhibitors, any new small lesions in the lung should be carefully evaluated for the presence of pneumonitis⁽²¹⁾. If noninfectious pneumonitis diagnosed on the basis of clinical and radiological

findings any medical intervention, treatment suspension or dose reduction varies according to the severity of disease ⁽²¹⁾.

A retrospective, centralized review of serial CT scans and corresponding clinical data of 64 patients at Memorial Sloan–Kettering Cancer Center, New York (MSK) of advanced non–small cell lung carcinoma treated with 10 mg oral daily everolimus in a phase II clinical study showed radiological evidence of pneumonitis in 24 patients. Among them, pneumonitis was suspected as possible in 12 patients and probable in 4 patients related to everolimus. Most common manifestations were focal areas of consolidation at lung bases or ground glass opacity. It was graded 1 or 2 in 12 patients and 4 patients have higher grades. In most of them, pneumonitis recovered at same or low grade with discontinuation of therapy⁽²²⁾.

Retrospective collected cases of pneumonitis induced by sirolimus or everolimus among 1471 adult cadaveric renal transplant recipients who were grafted at single institution from 1980–2008, 205 patients were switched from calcineurin inhibitors to sirolimus (n=88) or to everolimus (n=117). Six patients (2.9%) have pneumonitis, 1 was associated with sirolimus and 5 with everolimus. Median time from conversion to pneumonitis onset was 34 days in 4 patients (range 24–46 days) and 491 days in 2 patients (range 544–528 days). The most common symptoms were dry cough (n=6), fever (n=5) and dyspnea (n=4). Imaging test revealed lower lobe involvement in all patients. 5 patients received steroids and all patients recovered after drug withdrawal⁽²³⁾. Prospective analysis⁽¹⁰⁾ by blinded central review assessing incidence, radiographic pattern, management and outcome of pneumonitis among 274 patients treated with everolimus in RECORD – 1 trial, showed incidence of clinical pneumonitis in 13.5% (n=37) of patients in everolimus group as compared to 0% in placebo group. All adverse events were graded according to national cancer institute common technology criteria for adverse events (NCI CTCAE)⁽²⁴⁾. 3.3% (n=9) were grade 1 (asymptomatic), 6.6% (n=18) were grade 2 (not interfering with daily living) and 3.6% (n=10) were grade 3 (interfering with daily living or oxygen indicated). No grade 4 (life threatening) pneumonitis was observed. Median time to occurrence was 108

days (range 24–257 d) in their series and in our case it was 118 days. Most of them presented with cough (51.4%) and dyspnea (43.2%) and 32.4% have both cough and dyspnea, similar to our case. Corticosteroid was initiated in 16 patients (43.2%), dose reduction in 20 patients (54%) and discontinuation of everolimus in 10 patients (27%), 3 with grade 2, 7 with grade 3. Complete reversibility was seen in 20 of 37 patients (54%) and partial reversibility in 3 patients (8%) during the follow up. There were 2 deaths in patients with grade 3 toxicity, 1 died with alveolar hemorrhage and candidal sepsis, other with progressive metastatic disease and ARDS. In this series there were higher numbers of new radiographic findings in everolimus group as compared to placebo group (38.9% vs 15.2%) in patients without clinical pneumonitis. Baseline radiographic abnormalities were present in 17% of all of those receiving everolimus and in 24% of those with clinical pneumonitis, but were noted in 50% of patients with grade 3 toxicity. The presence of baseline radiographic abnormalities contributing to an increased risk of serious toxicity previously has been noted for other drugs, notably with gefitinib, erlotinib, methotrexate, leflunomide, temsirolimus as well as with everolimus ^(22, 25–30). Other published case reports on noninfectious pneumonitis with everolimus therapy showed similar clinical and radiographic features ^(31, 32).

All patients treated with mTOR inhibitors should be warned to promptly report symptoms such as dyspnea or cough. Thoracic CT scan should be conducted every 12 weeks. This and previous reported cases highlights the importance to consider pulmonary toxicity in differential diagnosis of patients who are on Everolimus and presenting with respiratory symptoms or pulmonary lesions. Given the potential rapid and fatal deterioration of mTOR inhibitor associated pulmonary toxicity, prompt recognition of the syndrome and withdrawal of the offending drug may be lifesaving. Recommendations of panel^(10, 21) for the management of interstitial pneumonitis according to severity of clinical manifestation are described in detail in (Table. 1).

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