Everolimus-induced interstitial lung disease in patient with metastatic renal cell carcinoma – case report and literature review

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ABSTRACT

We present a case of a 70-year-old man with metastatic renal cell carcinoma treated with second-line everolimus after rapid progression on first-line tyrosine kinase inhibitor, in whom a side effect of the therapy occurred in the form of a drug-induced interstitial lung disease. We also provide a review of the literature concerning opinions on incidence, clinical picture, consequences and management of the complication discussed.

KEYWORDS: everolimus, interstitial lung disease, metastatic renal cell carcinoma

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SUBJECT PRESENTATION ON THE BASIS OF LITERATURE

Everolimus is a selective inhibitor of mTOR (mammalian target of rapamycin), which in turn is a serine/threonine protein kinase whose activity increases in certain human malignancies [1].

Everolimus is registered in Poland for treatment of:

- advanced renal cell carcinoma – for patients whose disease progressed during or after therapy with anti-VEGF (vascular endothelial growth factor),
- advanced breast cancer with hormone receptor expression, without overexpression of HER-2/neu, in combination with exemestane in postmenopausal women without symptomatic visceral metastases, upon relapse or progression after treatment with non-steroidal aromatase inhibitor
- unresectable or metastatic highly or moderately differentiated neuroendocrine tumors of the pancreas in adult patients with progressive disease.

Everolimus is also used worldwide in treatment of angiomyolipoma in the course of tuberous sclerosis and subependymal giant cell astrocytoma (SEGA, formerly astrocytoma tuberous sclerosis), in prevention of kidney and liver transplant rejection as well as for coating coronary stents.

Interstitial lung disease is a class effect of derivatives of rapamycin (sirolimus, everolimus, temsirolimus). The mechanism of development of this side effect is not clear. One hypothesis postulates hypersensitivity reaction related to T lymphocytes. Scarce data suggests immunological mechanism. A few performed lung biopsies revealed histologic pattern of organizing pneumonia, granulomatous inflammation, lymphocytic infiltration, vasculitis and lymphocytosis in broncho-alveolar lavage fluid [2–4]. In a population undergoing renal transplantation and receiving everolimus, it was found that, apart from the pattern of organizing pneumonia, a histologic pattern of NSIP (non-specific interstitial pneumonia) occurred, or the coexistence of both types of changes [5]. The literature also reports DAH (diffuse alveolar hemorrhage) induced by everolimus [6].

Patients with this complication may be asymptomatic or exhibit nonspecific respiratory symptoms, such as cough, dyspnea, hypoxemia, hemoptysis and, rarely, hydrothorax. Most frequently observed radiological changes are: areas of ground glass and focal parenchymal opacities located mainly in the lower lobes [2, 7]. In a meta-analysis which included 2,233 patients treated for breast cancer, kidney cancer and neuroendocrine tumors of the pancreas, the incidence of pulmonary complications, taking into account all degrees of severity, was rated at 10.4% for temsirolimus and 2.4% for everolimus. There was no correlation between the occurrence of pulmonary toxicity and the occurrence of metastases in the lungs or intensity of the medication exposure [8]. In the Japanese population, toxicity profile of everolimus differs from these observed in the Caucasian population. The prevalence of interstitial pneumonia in patients treated with everolimus due to metastatic renal cell cancer is 22% and is the most common cause of treatment discontinuation [9]. In a Korean study, the incidence of lung lesions was not significantly different from that being reported in the Western population, but the clinical manifestation was much more severe and included fatalities [10].

A registration study of everolimus in metastatic clear cell renal cell carcinoma – RECORD-1 (Renal Cell Cancer Treatment with Oral RAD001 Given Daily) – found that approximately 14% of patients were diagnosed with non-infectious pneumonitis (9 patients – grade 1, 18 patients – grade 2, 10 patients – grade 3, grade 4 changes were not found). The beginning of lung lesions formation was observed within 2–6 months after initiation of everolimus therapy. The dosage of the medication was reduced in 2 patients with changes in grade 1 and in 12 patients with changes in grade 2; the therapy was ended in 3 patients with severe changes grade 2 and in the majority of patients with grade 3 lesions. Systemic glucocorticosteroid therapy was applied in the majority of patients with lesions grade 2 and in all with grade 3. Two patients died in the course of changes in grade 3 [2, 11, 12].

On this basis, an expert panel recommends that patients who initially present with respiratory symptoms (cough, shortness of breath at rest or on exertion) and patients with diagnosed numerous lung metastases should have respiratory function tests performed, including diffusing capacity of the lung for carbon monoxide (DLCO) and blood oxygenation prior to everolimus usage. In the case of DLCO below 40% of the predicted value, medication should not be used until normal values are reached. Everolimus is not recommended for use in patients with pulmonary fibrosis and severe chronic obstructive pulmonary disease [2]. It has been shown that patients with metastatic clear cell renal cell carcinoma receiving everolimus exhibit a decrease of DLCO/VA (Diffusing Capacity/alveolar volume) over time. Its low values found in body

plethysmography are characteristic of pulmonary restrictive diseases. Unfortunately, it has not been proven that low baseline DLCO/VA or a change in the DLCO/VA over time correlate with the development of interstitial lung lesions during therapy and therapy effectiveness [13].

In the case of the parenchymal lung changes due to the immunosuppressive properties of the medication, infectious etiology (bacterial and fungal) should be excluded, as well as opportunistic infections (*Pneumocystis jiroveci*) and reactivation of pre-existing infection [2, 14–18].

CASE PRESENTATION

A 70-year-old male, non-smoker for the last 5 years (previously smoked approximately 25 pack-years), suffering from metabolic syndrome and chronic kidney disease (grade 3), with a diagnosis of clear cell renal cell carcinoma (type G2 according to Fuhrman grading system), after the right-sided nephrectomy (May 2010) preceded by a right renal artery embolization, with lytic metastatic bone changes, after the femur intramedullary stabilization in September 2010, was treated since June 2011 with 50 mg sunitinib in regimen 4 weeks on and 2 weeks off. An increased blood pressure during the therapy required modification of the antihypertensive treatment. After 6 months of treatment, the patient was admitted to the Department of Cardiology because of unstable angina; coronary angiography revealed changes in multiple coronary arteries, palliative angioplasty of the right coronary artery was performed. The computed tomography after 6 cycles of treatment revealed progression of the disease in the form of a new metastatic lesion in the segment 8 of the liver with a diameter of 21 mm. For this reason, treatment with sunitinib was ended.

In February 2012, therapy with everolimus 10 mg per day was started. Anemia grade 2 CTCAE and solitary kidney function impairment (creatinine 2 mg/dl, eGFR 35ml/min/1.73 m^2) were observed during therapy. Computed tomography performed after 3 cycles of treatment revealed multiple, scattered ground glass opacities in the parenchyma of both lungs. The patient did not display any respiratory symptoms, so the severity of changes was classified as 1 toxicity grade of CTCAE and everolimus therapy was continued without changing the dose. In subsequently performed tests, the picture of lung lesions was stable. However, with the emergence of general weakness, stomatitis 2 grade CTCAE, diarrhea 2 grade CTCAE and headaches in July 2012, the decision about dose reduction to 5 mg per day was made, with the patient's prior consent. Computed tomography performed after next 3 months showed partial regression of pulmonary lesions. Next imaging further illustrated the spontaneous regression of parenchymal changes in the lungs until they have completely disappeared in August 2013. Extrapulmonary metastases remained stable in radiographic imaging, so the treatment with everolimus (5 mg per day) was continued. Dose reduction resulted in a decrease of anemia and alleviation of other side effects of the medication. In November 2013, the areas of parenchymal ground glass opacities re-emerged in the parabasal segments of both lungs, still clinically silent. In February 2014, expansion of the changes was observed and after next 3 months, considerable spontaneous regression could be noted. The lesions were then located mainly in the upper right lobe and in the segment 3 of the left lung.

The third radiological image deterioration in a row was recorded in August 2014 – extensive ground glass changes with thickening intraalveolar partitions were located in the basal-rear segments of both lungs; changes in segment 3 regressed. It was the first time when the patient presented with productive cough, without fever, and decreased exercise tolerance. Physical examination revealed pulmonary crepitations on auscultation at the base of both lungs. Application of the amoxicillin with clavulanic acid did not bring improvement of the general condition. Everolimus therapy was discontinued and pulmonary diagnostics was performed in order to explain the nature of the changes. The inflammatory parameters (ESR, CRP, WBC) were not elevated. In bronchoscopy, there were no macroscopic features of inflammation and the specimen from transbronchial biopsy contained a fragment of lung parenchyma with areas of fibrosis and atelectasis as well as focal bronchiolisation. However, there were no cancer cells found. The fluid from broncho-alveolar lavage showed slightly increased percentage of neutrophil granulocytes, without an increase in the percentage of lymphocytes or eosinophils. The inoculation of bronchial secretions were used to breed strains of bacteria which appear in the flora of the oral cavity. The bronchial secretions did not contain mycobacterium tuberculosis. In body plethysmography, there were no signs of airway obstruction or restriction, DLCO in the normal range. A follow-up computed tomography performed 8 weeks after interruption of everolimus revealed complete regression of the observed pulmonary changes.

Everolimus therapy 5 mg per day was resumed; computed tomography carried out after 3 months of treatment showed

scarce areas of ground glass opacities in the perihilar region of the right lung, the patient denied respiratory ailments, inflammation parameters remained low, so the therapy was continued. The patient is now after 32 cycles of treatment with everolimus, of which 29 were given in the dose reduced to 5 mg per day. Everolimus therapy has allowed to achieve almost three-year stabilization of the renal cancer so far and a good quality of life.

TREATMENT OF EVEROLIMUS-INDUCED INTERSTITIAL LUNG DISEASE BASED ON LITERATURE

The treatment strategy of interstitial lung disease caused by exposure to everolimus should depend on its severity (tab. 1). In the situation when only radiological lesions are present without coexistence of clinical symptoms, the patient may continue treatment at the previous dose. The occurrence of symptoms should always result in an interruption of the treatment which can be continued after the disappearance of symptoms and radiological changes. It has been shown that the use of systemic glucocorticosteroids causes regression of everolimus-induced interstitial disease, but their application should be conditional on reaching a diagnosis excluding infectious etiology (especially *Pneumocystis jiroveci*) [11, 19].

It has been observed that the occurrence of interstitial lung disease as a complication of everolimus therapy in patients with clear cell renal cell carcinoma correlates with a significantly longer duration of treatment with this medication and longer overall survival. Therefore, it is probably a good predictor of clinical response to everolimus [20, 21].

SUMMARY

The presented case of a man with metastatic clear cell renal cell carcinoma treated with first line sunitinib with rapid progression, then with everolimus for almost three years with stabilization of the disease according to RECIST, supports the theory of interstitial lung disease during treatment with mTOR inhibitor being a favorable response marker. Progression-free survival (PFS) for our patient by far exceeds the median PFS reported in the registration study amounting to 5.42 months (95% confidence interval [CI]: 4.30, 5.82) for patients receiving everolimus after first line tyrosine kinase inhibitor therapy [12].

Everolimus was well tolerated by the patient and pulmonary toxicity did not exceed the 2 grade CTCAE.

Interpreting radiological changes observed during the treatment with mTOR inhibitors may be difficult and raising oncologist's concern. Extremely important is the correlation with respiratory symptoms. In doubtful cases, it is necessary to perform pulmonary diagnostics in order to exclude respiratory infection or progression of the underlying disease.

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TABLE 1.
Therapeutic method algorithm [11].

The degree of toxicity	Type of intervention	Diagnostics	Everolimus dose modification
1. Radiological changes	Intervention not required	Imaging* and respiratory function tests** every 2 cycles until resolution	Not required
2. Radiological changes + clinical symptoms of moderate intensity	Symptomatic treatment, SGCs*** – to be considered in the case of a persistent, tiring cough	Imaging and respiratory function tests every cycle until resolution, bronchoscopy to be considered	Dose reduction until symptoms resolve. If after 3 weeks there is still no improvement or if the symptoms are exhausting – stop the treatment
3. Radiological changes + severe clinical symptoms	After excluding an infection – administer SGCs, reduce dose depending on the clinical situation	Imaging and respiratory function tests every cycle until resolution, bronchoscopy strongly recommended	Discontinuation of the therapy until clinical signs have resolved; re-inclusion of the medication at a reduced dose
4. Life-threatening complications	After excluding an infection – administer SGCs, reduce dose depending on the clinical situation	Imaging and respiratory function tests every cycle until resolution, bronchoscopy strongly recommended	Therapy termination

* computed tomography or chest X-ray if the changes are visible on it
** saturation at rest, spirometry, DLCO
*** systemic glucocorticosteroids

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Authors' contributions:
Agnieszka Buraczewska: 90%, Joanna Kardas: 10%.