Patterns of Interstitial Lung Disease During Everolimus Treatment in Patients with Metastatic Renal Cell Carcinoma

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Objective: To elucidate the patterns of interstitial lung disease during everolimus treatment in patients with metastatic renal cell carcinoma, we reviewed seven cases of everolimus-induced interstitial lung disease.

Methods: Seven patients with metastatic renal cell carcinoma, which continued to progress despite treatment with sunitinib or sorafenib, developed interstitial lung disease after treatment with everolimus.

Results: Chest X-ray demonstrated diffuse infiltrates in lung fields, and chest computed tomography showed bilateral reticular and ground-glass opacities. Serum levels of lactate dehydrogenase (7/7), C-reactive protein (6/7), pulmonary surfactant associated protein D (1/7) and Krebs von den Lungen 6 (5/7) were elevated. The bronchoalveolar lavage fluid obtained from four patients with Grade 3 interstitial lung disease showed lymphocytosis. The transbronchial lung biopsy specimens showed interstitial lymphocytic infiltration and septal thickening of alveolar walls. In two cases with mild interstitial lung disease, the everolimus therapy was successfully continued. In four cases with Grade 3 interstitial lung disease, the drug was discontinued and steroid therapy was initiated. Pulmonary symptoms and radiological abnormalities resolved within 2 months.

Conclusions: Serum Krebs von den Lungen 6 was elevated compared with baseline in all cases with interstitial lung disease. Some patients who developed mild interstitial lung disease during everolimus treatment could continue to receive the treatment. Even when severe interstitial lung disease developed, withdrawal of the drug and short-term use of high-dose steroids resulted in rapid recovery. Prompt recognition of interstitial lung disease exacerbation as well as exclusion of progressive disease or infection is of primary importance.

Key words: renal cell carcinoma – everolimus – interstitial lung disease

INTRODUCTION

Everolimus (RAD001, Afinitor®; Novartis) is an orally administered inhibitor of the mammalian target of rapamycin (mTOR) and was the first agent to receive approval in the USA (March 2009), Europe (August 2009) and Japan (January 2010) for the treatment of unresectable or metastatic renal cell carcinoma (mRCC). It affects cancer through novel pharmacological mechanisms such as the inhibition of mTOR, which has a role in cell growth, proliferation, cell survival and angiogenesis. Several clinical studies suggest that the drug is well tolerated and possesses a fairly effective antitumor activity, especially after vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy has failed (1,2). The subjective toxicities
frequently seen in patients assigned to everolimus were stomatitis or mucosal inflammation, rash, asthenia, diarrhea and nausea—mostly Grade 1 or 2 (1, 2). Although everolimus was recognized as a relatively safe oral anti-cancer agent, pulmonary toxicity [interstitial lung disease (ILD)] has been reported as a serious adverse effect (2). The incidence of everolimus-induced ILD in patients treated for advanced clear cell RCC was reported to be 11.7% in a second-line Phase III study (2). However, the mechanisms by which everolimus induces ILD are not clear, and no clinical/physiological analysis of this problem has been reported. We report here seven cases of ILD induced by everolimus during the treatment of mRCC. We obtained and analyzed bronchoalveolar lavage (BAL) fluids and transbronchial lung biopsies (TBLBs) from those patients who presented Grade 3 ILD. These data provide clinical and biological information needed to enhance our understanding of everolimus-induced ILD.

PATIENTS AND METHODS

Seven out of 11 patients with mRCC, which continued to progress despite treatment with sunitinib or sorafenib, developed ILD after treatment with everolimus 5–10 mg once daily. They fulfilled the following criteria for presumed everolimus-associated ILD: exposure to everolimus before the onset of pulmonary symptoms, exclusion of infection or alternative pulmonary disease, and ILD with organizing pneumonia pattern on chest computed tomography (CT). The everolimus-associated ILD was graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0.

RESULTS

PATIENT CHARACTERISTICS

Five male and two female Japanese patients, who received everolimus therapy for metastatic clear cell RCC, with a mean age of 69.1 years (range 57–77) were included. All patients had Karnofsky performance status 70–100 and previous treatment with VEGFR TKI. The average time to ILD onset was 66.3 days (range 40–125). Patient characteristics are shown in Table 1.

RADIOLOGICAL EXAMINATION

Chest radiography demonstrated diffuse infiltrates in both lung fields (Fig. 1A). CT of the chest showed bilateral reticular and ground-glass opacities. These opacities predominantly involved the lower lobe (Fig. 1B).

LABORATORY FINDINGS

Serum levels of lactate dehydrogenase (7/7), C-reactive protein (6/7), pulmonary surfactant-associated protein D (SPD) (1/7) and KL-6 (5/7), but not peripheral white blood cell counts, were elevated. Four patients with Grade 3 ILD had neither cytomegalovirus antigen nor elevated serum β-D-glucan. The drug lymphocyte stimulation test with everolimus in four patients with Grade 3 ILD yielded negative results in peripheral blood samples (Table 2).
Culture of BAL fluid samples from four patients with Grade 3 ILD proved negative for bacterial and fungal pathogens. No tumor cells were detected in any BAL fluid. Lymphocytes were predominant in four patients and eosinophils in two patients (Table 2). The CD4:CD8 ratio varied among the patients (Table 2). TBLB specimens from three patients with Grade 3 ILD showed a thickening of alveolar walls and lymphocytic interstitial inflammation, but no hemosiderin-laden macrophages (Fig. 2).

**Management and Prognosis**

Two of the seven patients experienced pulmonary symptoms. Dry cough, dyspnea and fatigue were common to those patients. After discontinuation of everolimus, pulmonary complications were spontaneously resolved in one patient but exacerbated in the remaining case. Five out of the seven patients were clinically asymptomatic, although ILD was apparent on routine chest CT. The everolimus therapy was continued since the ILD was asymptomatic in those five cases. The everolimus therapy succeeded in two of the five cases, but was unsuccessful (i.e. Grade 3 ILD developed) in the remaining three. Dryness and cough are common symptoms of ILD exacerbation. Finally, we experienced four cases of Grade 3 ILD. The pleural effusion was seen in three patients. The average time to the exacerbation of ILD was 38.3 days (range 5–123). After diagnosis of Grade 3 ILD, everolimus therapy was discontinued immediately and all four patients were treated with corticosteroids (1 mg/kg of body weight per day). After starting corticosteroid therapy, clinical symptoms resolved within 2 weeks and interstitial shadows began to improve gradually in all four patients. Corticosteroids were thereafter reduced to a maintenance dose and discontinued after 1 month. Chest radiography and CT showed disappearance of ILD within 2 months in all four patients.

**Discussion**

The precise mechanism by which everolimus induces ILD is not fully understood; however, findings of previous studies on mTOR inhibitors lead to the speculation that a direct, dose-dependent toxicity and an autoimmune response or delayed hypersensitivity reaction to everolimus underlie pathogenesis (3,4). Since mTOR inhibitors are widely used as immunosuppressants, several distinct types of lung toxicity associated with those drugs, including lymphocytic interstitial pneumonitis, lymphocytic alveolitis, bronchiolitis obliterans with organizing pneumonia, focal pulmonary fibrosis, diffuse alveolar hemorrhage or a combination of these entities, have been reported in solid organ transplant recipients (3–5). In our study, BAL lymphocytosis was present in all patients with Grade 3 ILD. Histological examination of TBLB specimens demonstrated the presence of interstitial lymphocytic infiltration with septal thickening of alveolar walls mainly. Small foci of damaged alveoli with fibrinous exudates or fibroblastic nodule in alveolar spaces were also observed. These findings are consistent with previous reports in heart and renal transplant recipients who developed mTOR inhibitor-associated ILD (6–8).

### Table 2. Laboratory data and analysis of bronchoalveolar lavage fluid

<table>
<thead>
<tr>
<th>Patient</th>
<th>WBC (/mm³)</th>
<th>LDH (IU/l)</th>
<th>CRP (mg/dl)</th>
<th>SPD (ng/ml) (ILD⁺)</th>
<th>KL-6 (U/ml) (ILD⁻/ILD⁺)</th>
<th>DLST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4200</td>
<td>261</td>
<td>0.80</td>
<td>99</td>
<td>469/1544</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>5000</td>
<td>294</td>
<td>5.47</td>
<td>30</td>
<td>322/614</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>6100</td>
<td>267</td>
<td>0.27</td>
<td>102</td>
<td>162/421</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
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<td>458</td>
<td>4.11</td>
<td>61</td>
<td>404/1227</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
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<td>291</td>
<td>1.00</td>
<td>38</td>
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</tr>
<tr>
<td>6</td>
<td>5100</td>
<td>642</td>
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</tr>
<tr>
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<td>273</td>
<td>5.96</td>
<td>78</td>
<td>204/446</td>
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</tbody>
</table>

WBC, white blood cells; LDH, lactate dehydrogenase (<220); CRP, C-reactive protein (<0.35); SPD, surfactant protein D (<110); KL-6, Krebs von den Lungen 6 (<500); DLST, drug lymphocyte stimulation test; MAC, macrophages; Lymph, lymphocytes; Neu, neutrophils; Eosino, eosinophils.
cases was provoked by relatively high-dose everolimus therapy (10 mg/day) compared with the dose used in immunosuppressant regimens, all our cases were successfully treated by cessation of the drug and initiation of high-dose steroid therapy. These cases highlight the importance of recognizing ILD exacerbation promptly during everolimus therapy for mRCC.

According to the data reported for everolimus in mRCC, the incidence of everolimus-induced ILD appears to be higher in Japanese patients, at 27 versus 11% worldwide (10). An increased genetic susceptibility to everolimus-induced ILD in the Japanese population is not surprising because genetic susceptibility to other TKI-induced ILDs has already been proposed. In non-small cell lung carcinoma treatment, the rate of ILD associated with gefitinib (an epidermal growth factor receptor—TKI) is higher in Japan than elsewhere (11,12). Moreover, gefitinib-induced ILD tends to be irreversible, severe and fatal once diffuse alveolar damage develops (13). In this study, everolimus-induced ILD became severe in three cases, but readily disappeared on cessation of the drug and treatment with corticosteroids. Thus, everolimus-induced ILD differs from gefitinib-induced ILD, especially in its reversibility.

In our study, serum KL-6 was elevated compared with baseline in all cases with ILD. KL-6 is a high-molecular-weight glycoprotein classified in humans as MUC1 mucin (14). Serum levels of KL-6 are elevated in patients with different types of ILD (15). KL-6 develops in a type II alveolar epithelial cell, in a bronchial epithelial cell and in a bronchus gland cell. The expression of KL-6 increases in the hyperplasia of the type II of alveolus epithelial cell in ILD (16). Our data indicated that serum KL-6 would increase in RCC patients which developed ILD during everolimus treatment. Further studies are needed to determine whether KL-6 will prove to be a useful indicator of ILD exacerbation in these patients.

To summarize, in some cases of mRCC that develop asymptomatic everolimus-induced ILD, everolimus therapy could be continued. Even when exacerbated, ILD could be successfully treated by cessation of the drug and initiation of steroid therapy. Prompt recognition of ILD exacerbation, as well as exclusion of progressive pulmonary disease or infection, is of primary importance. Serum KL-6 was elevated compared with baseline in all cases with ILD.

Conflict of interest statement
None declared.

References


