CASE REPORT

A case of metastatic renal cell carcinoma showing complete remission after cytoreductive nephrectomy followed by temsirolimus

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Abstract Here, we present a case report of a patient with poor-risk advanced renal cell carcinoma who had a complete remission after cytoreductive nephrectomy followed by temsirolimus. A 67-year-old woman was diagnosed with advanced renal cell carcinoma, stage pT3aN2M1 in April 2013. In the Memorial Sloan-Kettering Cancer Center criteria, she had three prognostic factors and was classified into the poor-risk category. After 23 weeks of treatment with temsirolimus, complete remission was achieved. Temsirolimus treatment was discontinued after 23 weeks because of grade 3 toxicity noninfectious pneumonitis. Five months after beginning steroid treatment without temsirolimus, a CT scan showed no new metastatic lesion or progression of disease. This was a very rare case with achievement of a complete remission after cytoreductive nephrectomy followed by temsirolimus.

Keywords Poor-risk renal cell carcinoma · Temsirolimus · Complete remission

Introduction

Temsirolimus, a specific inhibitor of mammalian target of rapamycin kinase (mTOR), prevents progression of the cell cycle through inhibition of mTOR-dependent protein

translation. In addition, it also has potent antiangiogenic effects [1]. In a global multicenter phase 3 trial (ARCC), it was found that temsirolimus alone improved overall survival among patients with metastatic renal cell carcinoma and a poor prognosis compared with temsirolimus combined with IFN- α and INF- α alone [2]. On the basis of these results, temsirolimus is recommended as a first-line treatment for patients having metastatic renal cell carcinoma with a poor prognosis by the National Comprehensive Cancer Network [3] and the European Association of Urology Renal Cell Cancer Guidelines [4]. However, in this ARCC phase 3 trial, the objective response rate to temsirolimus treatment was only 8.6 % [2]. In other reports, the objective response rates to temsirolimus treatment ranged from 0 to 11 % [5–7]. In these reports, no patients with metastatic renal cell carcinoma had a complete response after such treatment. Here, we report a patient with poor-risk advanced renal cell carcinoma who achieved a complete remission after cytoreductive nephrectomy followed by temsirolimus.

Case report

A 67-year-old woman presented at the Department of Internal Medicine with dizziness in 2012. Decreased hemoglobin (8.1 g/dl) and increased corrected serum calcium (10.0 mg/dl) were observed. Contrast-enhanced computed tomography (CT) showed a left renal tumor measuring 12.2 cm × 9.1 cm, supraclavicular lymphadenopathy, paraaortic lymphadenopathy and aortocaval lymphadenopathy (Fig. 1a, e). On magnetic resonance imaging (MRI), there was no brain metastasis. She was referred to our department for treatment of the left renal tumor and underwent radical nephrectomy in April 2013.

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Fig. 1 Computed tomography. Responses to temsirolimus treatment of supraclavicular lymphadenopathy (a–d), paraaortic lymphadenopathy and aortocaval lymphadenopathy (e–h). **a, e** At baseline, **b, f** after 16 weeks of temsirolimus treatment, **c, g** after 23 weeks of temsirolimus treatment and **d, h** 5 months of steroid treatment without temsirolimus. Noninfectious pneumonitis was observed after **i** 23 weeks of temsirolimus treatment and **j** 5 months of steroid treatment

The pathological diagnosis was confirmed to be clear cell RCC, G3, pT3a, INFb, ly0, v1 and she was diagnosed with advanced renal cell carcinoma, stage pT3aN2M1. In the Memorial Sloan-Kettering Cancer Center (MSKCC; NY, USA) criteria, she had three prognostic factors (decreased hemoglobin, increased calcium and time from diagnosis to treatment of less than 12 months). Thus, she was classified into the poor-risk category.

We decided to treat her with temsirolimus according to the recommendations of several guidelines for poor-risk metastatic renal cell carcinoma [2, 3]. The concentrations of serum Klebs von der Lungen-6 (KL-6), surfactant protein (SP)-A and SP-D were 451 U/l, 24.6 ng/ml and 69.7 ng/ml, respectively, before treatment with temsirolimus. She started intravenous temsirolimus 25 mg/m² weekly from May 2013. After 16 weeks of treatment, a CT scan showed that she had achieved a partial response and the reduction rate was 53.8 % compared to the baseline (Fig. 1b, f). The scan revealed an interstitial change of the right lower pole of the lung. Because she had an objective response to the treatment and the adverse pulmonary interstitial change was grade 1, we decided to continue the treatment at the same dose.

Following 23 weeks of treatment with temsirolimus, she had an acute onset of coughing and high fever. A CT scan revealed worsening of the interstitial change of the right middle, lower pole and left lower pole of the lungs (Fig. 1i). However, the supraclavicular lymphadenopathy, paraaortic lymphadenopathy and aortocaval lymphadenopathy had disappeared (Fig. 1c, g). The concentrations of serum KL-6, SP-A and SP-D were 1120 U/l, 117 ng/ml and 302 ng/ml, respectively. These data showed that the serum KL-6, SP-A and SP-D levels were abnormal and higher than before treatment with temsirolimus. Tests for *Legionella* urinary antigen, serum *cytomegalovirus* antigen and serum *pneumococcal* antibodies were all negative. The level of β -D-glucan was <6.0 pg/ml. Sputum culture revealed no pathogens in the mouth. According to these examinations, the respiratory internal medicine department diagnosed her condition as temsirolimus-induced noninfectious interstitial pneumonitis. Temsirolimus was discontinued and steroid pulse treatment was begun by that department. Five months after the steroid treatment without temsirolimus began, a CT scan showed no new

metastatic lesion or progression of disease (Fig. 1d, h). The temsirolimus-induced noninfectious interstitial pneumonitis was improved by the steroid pulse treatment (Fig. 1j). The concentrations of serum KL-6, SP-A and SP-D, which were 189 U/l, 41.8 ng/ml and 69.0 ng/ml, respectively, had become normal again. In March 2016, she had no new metastatic lesion or progression of disease 27 months after discontinuing temsirolimus.

Discussion

According to the MSKCC criteria, 11–22 % of metastatic renal cell carcinoma patients have three or more risk factors and are classified into the poor-risk category. The prognoses of these patients are poor, with a median survival time of 4 months following immunotherapy [8, 9]. In the international phase 3 ARCC trial, the results showed that metastatic renal cell carcinoma patients with poor prognoses who received temsirolimus alone had longer overall survival ($p = 0.008$) and progression-free survival ($p < 0.001$) than patients who received IFN- α [2]. Based on these results, temsirolimus is recommended as the first treatment choice for patients with poor-risk metastatic renal cell carcinoma in the National Comprehensive Cancer Network [3] and European Association of Urology guidelines for kidney cancer [4].

In the ARCC trial, the objective response rate for treatment with temsirolimus was low (8.6 %). By contrast, the proportion of stable disease was 32.1 % [2]. Ashar et al. reported the efficacy of temsirolimus in 38 previously untreated patients with renal tumors and poor-intermediate prognoses. In that study, although 11 and 34 % of all patients achieved a partial response and stable disease, respectively, no patient achieved a complete response [10]. In a phase 2 study of East Asian patients treated with temsirolimus, no patient had a complete response, though 11 % had partial responses [6]. Miyake et al. reported a retrospective study of the use of temsirolimus by 55 consecutive metastatic renal cell carcinoma patients in Japan. The objective response rates were 0, 7.3, 80.0 and 12.7 % for complete response, partial response, stable disease for at least 6 weeks and progression of disease, respectively [5]. These results showed that the drug was mainly efficacious for continued stable disease rather than the reduction of tumor volume. Notably, however, our patient had a complete response following 23 weeks of treatment with temsirolimus. Furthermore, the complete response was still maintained 5 months after its discontinuation. In our patient, the corrected serum calcium level was 10.0 mg/dl before surgery and 10.3 mg/dl 1 week after surgery, indicating that her condition was very close to intermediate risk. Although it is very rare, spontaneous

regression of metastatic renal cell carcinoma has been reported [11, 12].

Noninfectious pneumonitis is typical in patients with temsirolimus treatment and sometimes the treatment is discontinued because of this adverse event, which occurs in 6–30 % patients undergoing this treatment [2, 5–7, 10, 13]. Some papers reported the relationship between noninfectious pneumonitis and the efficacy of temsirolimus. Dabydeen et al. retrospectively examined the clinical data from 46 patients with metastatic renal cell carcinoma treated with temsirolimus and everolimus [7]. In that report, stable disease was achieved in 86 % of those who developed radiographic pneumonitis compared to 44 % without pneumonitis ($p = 0.002$). Atkinson et al. reported 310 retrospectively studied patients with metastatic renal cell carcinoma who received temsirolimus and/or everolimus. Noninfectious pneumonitis developed in 12 % of the patients treated with the mTOR inhibitor, with a median time to radiological appearance of 62.5 (35–736) days. Patients who developed noninfectious pneumonitis had a significantly longer time on treatment (median 4.1 vs. 2 months) and overall survival (median 15.4 vs. 7.4 months) [13]. In our patient, noninfectious pneumonitis was observed in the early period following the beginning of the treatment. There was an inverse relation between the progression of the noninfectious pneumonitis and metastatic tumor size. Thus, the treatment might be more efficacious for patients who develop temsirolimus-related pneumonia than for those who do not. The reason why temsirolimus induces noninfectious pneumonitis remains unclear. With regard to the immune response, mTOR reconfigures the cellular metabolism and regulates the translation, cytokine responses, antigen presentation, macrophage polarization, and migration of cells [14].

In conclusion, we experienced a very rare case with achievement of a complete remission after cytoreductive nephrectomy followed by temsirolimus and the complete remission has continued for 27 months after discontinuation of the drug.

Compliance with ethical standards

Conflict of interest None declared.

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