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CASE REPORT

Longer recurrence-free survival in a patient with metastatic renal cell carcinoma treated with temsirolimus

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Key Clinical Message

Temsirolimus did not demonstrate an efficacy advantage compared with sorafenib as second-line therapy in patients with metastatic renal cell carcinoma (mRCC). Only a few patients achieved complete responses, and the median progression-free survival rate remains short. We report one patient with mRCC who had a continuing response to temsirolimus.

Keywords

Mammalian target of rapamycin, metastatic renal cell carcinoma, temsirolimus.

Introduction

The treatment of metastatic renal cell carcinoma (mRCC) has significantly improved due to the addition of targeted agents that inhibit elements of the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathway. The treatment with temsirolimus for advanced renal cell carcinoma (RCC) has shown efficacy and safety in a phase II study on cytokine refractory patients [1]. Temsirolimus is also considered to be the standard of care in first-line therapy of mRCC patients with a poor-risk prognosis. However, in a randomized phase III trial, temsirolimus did not demonstrate an efficacy advantage compared with sorafenib as second-line therapy after disease progression in patients treated with sunitinib for mRCC [2]. In addition, only a few patients achieved complete responses (CR) [3] and the median progression-free survival (PFS) rate remains relatively low in patients with mRCC who received temsirolimus [1, 2, 4]. Herein, we report one patient with mRCC who had a continuing response to temsirolimus for more than 3 years after failure of treatment with tyrosine kinase inhibitors (TKIs).

Case Report

A 51-year-old Japanese man presented at a community hospital with a chief complaint of continuous low-grade fever. The patient had an abnormal chest X-ray and visited our hospital in October 2012. Laboratory evaluations revealed the following findings: hemoglobin, 7.2 g/dL (normal range: 13.5–17.5 g/dL), corrected calcium level, 10.6 mg/dL (normal range: 8.3–10.3 mg/dL), and C-reactive protein, 17.3 mg/dL (normal range: <0.3 mg/dL). Computed tomography (CT) revealed a hypervascular tumor (size, 9 × 8.5 cm) in the upper pole of the left kidney with multiple lung metastases (Fig. 1, 2A and B). The tumor was clinically diagnosed as a left renal cell carcinoma (RCC) and was classified as clinical T2bN2M1 according to the tumor–node–metastasis system [5].

The patient underwent open radical nephrectomy in December 2012. Pathological analysis identified a pT3a clear cell RCC of Fuhrman grade 3 with hemorrhage and necrotic tissue. In January 2013, the patient received sunitinib at 50 mg/day for 2 weeks of every 3-week cycle for the treatment of multiple lung metastases. After two cycles, a lung CT showed disease progression with lung

metastases, which increased in size (Fig. 3A and B). The patient received axitinib at 10 mg/day starting in March 2013. After 5 months of axitinib treatment, the patient achieved a complete response (CR) with lung metastases [5]. In February 2014, CT showed a mediastinal lymph node metastasis after a year of axitinib treatment (Fig. 4). The patient received temsirolimus at 25 mg/week beginning in March 2014. After 3 months of temsirolimus treatment, the patient achieved a CR with a mediastinal lymph node metastasis (Fig. 5). In November 2016, the treatment schedule of temsirolimus was changed from weekly to biweekly. To date, CT has shown no evidence of disease and treatment with temsirolimus is still ongoing. The patient did not experience any adverse events.

Discussion

mTOR is a highly conserved serine–threonine kinase and is activated through the phosphoinositide 3-kinase (PIK3)–Akt pathway after binding of the ligand to growth factor receptors [6]. Activation of the PIK3/Akt/mTOR pathway plays a critical role in the proliferation and survival of malignant cells and has been recognized as a valuable therapeutic target [6]. Temsirolimus is a prodrug and needs to be converted to its active metabolite, sirolimus, by CYP3A4 in the liver and has a half-life of approximately 13 h [1].

Based on a multicenter, randomized phase III trial [7], the European Association of Urology guidelines recommended temsirolimus as a first-line treatment in patients in the poor prognosis group according to the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria [8]. Median PFS and overall survival were 3.8 and 10.8 months, respectively [7]. Although TKIs or mTOR inhibitors are the standard therapy for mRCC, it is still difficult to achieve a CR in advanced RCC (aRCC) or mRCC. In fact, an objective response rate of only 8.6% has been reported among patients with poor prognosis mRCC receiving temsirolimus [7].

In a randomized phase III trial from investigating temsirolimus as second-line therapy, temsirolimus did not demonstrate an efficacy advantage compared with sorafenib as second-line therapy after disease progression in patients with mRCC who were receiving sunitinib [2]. Several studies showed that everolimus offers superior OS compared with temsirolimus after disease progression during TKI therapy for patients with mRCC, although both agents were associated with similar response rates and PFS [9, 10]. Iacovelli et al. reported that everolimus decreased the risk of death by 26% over temsirolimus [10]. Recent studies have demonstrated that cabozantinib and nivolumab are superior to everolimus after progression during initial TKI therapy. Therefore, everolimus may be considered a treatment option as third- or fourth-line therapy [11, 12].

To date, the optimal third-line treatment has not been established. Jonasch et al. investigated current practice patterns, including the selection of first- and second-line therapy and treatment sequences, for patients with mRCC [13]. A total of 433 patients who received second-line therapy were enrolled in this study. Only 21% of the

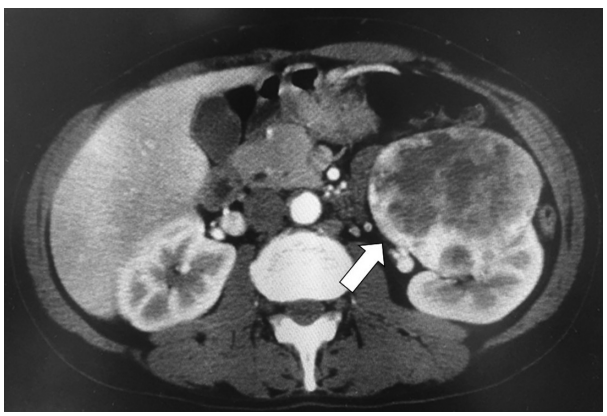

Figure 1. Abdominal computed tomography revealed a hypervascular tumor, measuring 9 × 8.5 cm, in the upper pole of the left kidney (arrow).

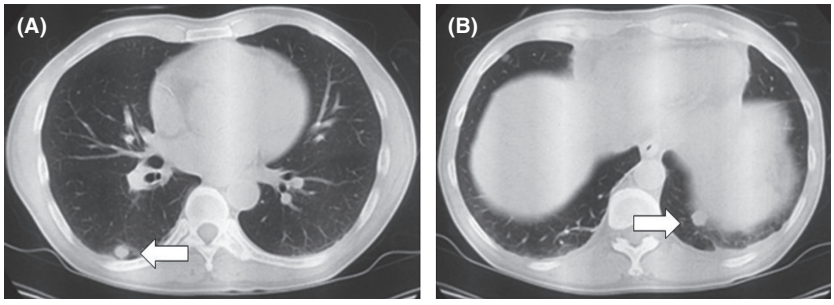

Figure 2. (A and B) Thoracic computed tomography revealed multiple lung metastases (arrow).

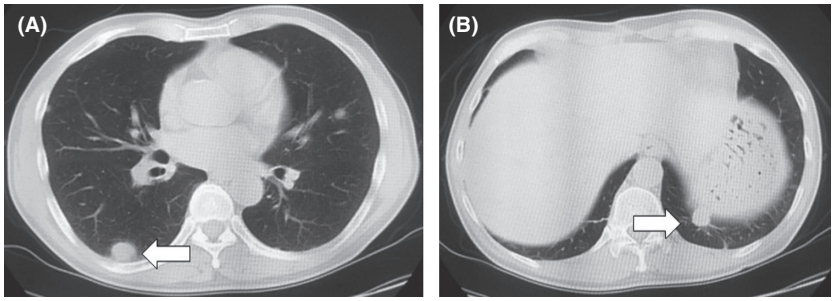

Figure 3. (A and B) Thoracic computed tomography revealed a disease progression with multiple lung metastases, which increased in size (arrow).

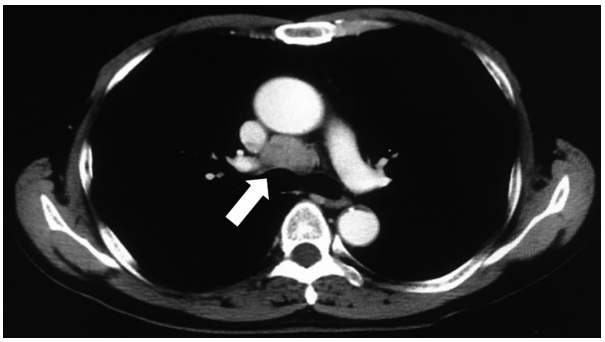

Figure 4. Thoracic computed tomography revealed a lymph node metastasis in the mediastinum (arrow).

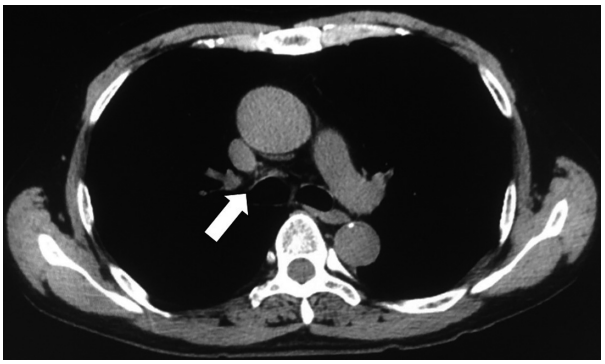

Figure 5. Thoracic computed tomography showed a complete response by RECIST criteria (arrow) [3].

patients received third-line therapy [13]. Of these, sunitinib–everolimus–bevacizumab was the most commonly used treatment sequence [13]. Wells et al. reported the use of targeted third-line therapy [14]. OS after cessation of second-line therapy was 14 months in patients who received third-line therapy, and 2.1 months for those not receiving third-line therapy ($P < 0.001$) [14]. However, only 3.2% of the patients were administered temsirolimus as a third-line therapy [14]. Thus, the frequency of use of temsirolimus for patients with aRCC or mRCC may decrease in the future. However, the toxicity profile of patients who received temsirolimus was remarkably favorable with no grade 3/4 adverse events other than those who received TKI [15]. In the present case report, although the patient who was administered axitinib as a second-line TKI treatment achieved complete response for lung metastases, CT showed mediastinal lymph node metastasis. Therefore, we selected temsirolimus as a third-line treatment.

Although many molecular-targeted drugs are available, the choice of the best drug depends on the clinical situation. Temsirolimus may be a useful and valuable treatment in patients with aRCC or mRCC who failed to respond to TKIs.

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Authorship

TS: evaluated the patient's medical records, wrote the article draft; TK: performed critical revisions of the text and figures, and is the corresponding author; HH: evaluated the patient's medical record; NT: performed the clinical evaluation of the patient and contributed to the writing process; SN: operated the patient, obtained the patient's consent, and contributed to the writing process; CO: coordinated and supervised the writing process. All authors approved the final version of the manuscript.

Consent for Publication

Informed written consent was obtained from the patient.

Conflict of Interest

No conflict of interests to report.

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