A case of metastatic renal cell carcinoma treated effectively by gemcitabine and sunitinib

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KEY WORDS
- gemcitabine
- sunitinib
- metastatic renal cell carcinoma

ABSTRACT

A 60-year-old man with renal cell carcinoma developed lung metastases after treatment with left radical nephrectomy (pT3bN0M0, clear cell renal carcinoma, Fuhrman grade 3 >2). The patient received treatment with gemcitabine and interferon-α and achieved complete response after seven cycles of therapy. However, eight months later, local recurrence was discovered in the renal fossa. We changed the therapeutic strategy to sunitinib, a multi-target tyrosine kinase inhibitor. The patient achieved a complete response after twelve cycles of therapy. This case report illustrates the effective use of gemcitabine and sunitinib sequentially for a patient with metastatic renal cell carcinoma.

INTRODUCTION

Metastatic renal cell carcinoma (mRCC) is associated with poor prognosis, with a 5-year survival rate of 5-10% for patients with metastatic disease [1]. Immunoreactive cytokines have been the standard treatment for mRCC for the past two decades. Several reviews have reported response rates to cytokines as approximately 10-20% [1, 2]. Recently, available therapeutic options for mRCC have expanded with the development of agents targeting vascular endothelial growth factor (VEGF) receptors. Sunitinib is a novel multi-targeted receptor tyrosine kinase inhibitor (TKI) with response rates of 30-40% for mRCC. However, mRCC remains incurable with a median progression-free survival of 11 months [3, 4]. In Japan we could not use TKI until 2008, so when the patient exhibited resistance to immunotherapy we changed our therapeutic strategy to administering gemcitabine. Gemcitabine, a nucleoside analogue, has been reported as having a positive response rate of 17-31% [5, 6]. We report on one patient who has had a persistent complete response after treatment with gemcitabine and sunitinib sequentially.

CASE REPORT

A 60-year-old male patient was diagnosed with renal cell carcinoma (RCC) in the lower pole of the left kidney and underwent open radical nephrectomy in December 2006. The resected specimen was pathologically diagnosed as clear cell RCC, pT3bN0M0, Fuhrman nuclear grade 3 >2, and positive for microscopic venous invasion. The patient received interferon-α (IFN-α) by intramuscular injection (6 × 10^6 IU Sumiferon® per day; Dainippon Sumitomo Pharma, Osaka, Japan) three times per week as postoperative adjuvant therapy for six months. In June 2007, a follow-up computed tomography (CT) scan revealed disease recurrence in multiple lung metastases. Interleukin-2 (IL-2) monotherapy (0.7 × 10^6 U Immunace® per day; Shionogi & Co., Ltd., Osaka, Japan) was started twice per week for 2 months. However, multiple lung metastases increased, so the dose of IL-2 was increased to 1.4 × 10^6 U Immunace® per day according to the same schedule. Two months after the dose increase, progression of the lung metastases was recognized (Fig. 1a, b). Zustovich et al. reported the efficacy and safety of the combination therapy with gemcitabine and immunotherapy for mRCC in a phase II study in 2006, we changed the therapeutic regimen to gemcitabine and IFN-α therapy (GI) [6]. Gemcitabine (1500 mg) was administered intravenously for 30 min over a 28-day period (1 cycle) comprising three consecutive weeks of treatment (administration on day 1, 8, and 15) followed by one week of rest, and IFN-α by intramuscular injection (3 × 10^6 IU Sumiferon® per day) twice per week continuously. The response was assessed during each cycle for the first two cycles and thereafter every other cycle with CT scan and evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST).

A CT scan performed after seven cycles of GI therapy showed nearly 80% shrinkage compared with the baseline tumor measurements (Fig. 1c, d). The largest tumor of the multiple lung metastases had become a scar organization, and the other tumors had disappeared completely. Because we considered these developments as a complete response (CR), we had stopped the therapy and observed carefully. In June 2009, follow-up CT scan revealed local recurrence in the renal fossa (Fig. 2a, b). Treatment was begun with sunitinib, given orally at a dose of 50 mg/day on a 4-week-on/2-week-off schedule. In the first therapy cycle, grade IV thrombocytopenia was found, requiring a dose reduction to 37.5 mg/day after one cycle. In the second therapy cycle, grade 3 neutropenia, grade 3 hypertension, and grade 2 renal dysfunction were found, requiring a dose reduction to 25 mg/day after two cycles. The patient had achieved a partial response (50% shrinkage) by completion of the second therapy cycle. Sunitinib was continued; CT scan after twelve cycles of therapy showed CR compared with the baseline tumor measurements (Fig. 2c, d). The patient continued therapy with sunitinib for 22 months. However, because of the development of grade 3 renal dysfunction and grade 2 hypothyroidism, the therapy was terminated and CR has persisted for 12 months to date.

DISCUSSION

In this report, we describe one patient with mRCC who had developed lung metastases after radical nephrectomy. The patient experienced disease progression while receiving IFN-α and IL-2 therapy. He was subsequently treated with GI therapy for seven cycles and achieved CR. However, eight months after the end of GI therapy, local recurrence in the renal fossa appeared. The patient was subsequently treated with sunitinib for 22 months and achieved CR that lasted more than 12 months.

In this patient, immunotherapies using cytokines such as IFN-α and IL-2 were ineffective. Several studies have reported
favorable oncological outcomes of immunotherapy, in particular when using IL-2, in Japanese patients with mRCC compared with patients of Western populations [7, 8]. In Japan, IL-2 and IFN-α have been used at doses of 0.7–2.1 × 10^6 U/day and 3–6 × 10^6 IU/day, respectively, which are much lower than those used in Europe. In this case it might have been more effective if we had increased the dose of immunotherapy or had used the combined treatment with IFN-α and IL-2.

Among the new drugs studied for treatment of mRCC, gemcitabine has shown appreciable response rates (17–31%) and a safe toxicity profile [5, 6]. In a phase I trial, Perez-Zinc et al. evaluated thirteen patients with mRCC who were treated with weekly gemcitabine (600 mg/m²) and subcutaneous IFN-α2b three times weekly on a 6-week-on/2-week-off schedule [9]. However, they concluded that this regimen appeared to be associated with severe hematologic toxicity and they did not recommend this schedule. On the other hand, in the preliminary results of a phase I trial in patients with solid tumors by Fuxius et al., it was concluded that the recommended regimen of gemcitabine and IFN-α2b was 1000 mg/m² gemcitabine given once weekly plus 5 × 10^6 IU IFN-α2b given 3 × weekly for three consecutive weeks every 28 days [10]. A phase II study of gemcitabine and immunotherapy conducted in a study population of 25 patients reported a partial response in four patients (17%) and stable disease in 12 patients (50%) [6]. Recently, a novel therapeutic approach using molecular targeted agents has evolved for the management of mRCC. In a phase II study of gemcitabine and sunitinib in patients with mRCC, an objective response rate of 42% was achieved [3]. Based on these findings, we changed our therapeutic strategy to administering sunitinib alone when local recurrence in the renal fossa appeared. Because of the adverse events that included neutropenia, hypertension, and renal dysfunction, a dose reduction to 25 mg/day after two cycles was required. However, both the GI therapy and the sunitinib were effective for the metastases in our case and the patient was fortunate to achieve CR of multiple metastatic sites.

Recently, the standard of care for patients with mRCC has changed to favor targeted therapy over immunotherapy. According to EAU guidelines for RCC, cytokine therapy does not improve survival after nephrectomy. Although there is no current data supporting the adjuvant therapy with targeting agents, three worldwide phase III randomized trials are ongoing. Tyrosine kinase inhibitors should be considered as first- or second-line treatment for mRCC patients and IFN-α monotherapy only remains as an option in selected patients for mRCC. Pilmack et al. suggested that VEGF targeted therapies are more effective at controlling existing sites of disease rather than preventing new metastases [11]. Currently, when patients exhibit resistance to sunitinib, we usually change our therapeutic strategy to another TKI such as sorafenib or an inhibitor of mammalian target of rapamycin (mTOR) kinase such as temsirolimus [12]. However, CRs are rarely reported and the vast majority of patients will experience disease progression.

Although gemcitabine is not strongly recommended in the guidelines, several reports studied the combination of gemcitabine and other anti-cancer-drugs (such as interferon, sorafenib, capecitabine, and sunitinib) [13, 14]. Pandya et al. proposed that the combination of gemcitabine and sunitinib in patients with mRCC might delay disease progression in some patients with mRCC [13]. Bellmunt et al. reported that the activity of a multi-targeted chemo-switch regimen (sorafenib, gemcitabine, and metronomic capecitabine) in mRCC as a first line therapy in a phase II study [14]. In their study, a partial response was achieved in 50% of patients and disease stability was achieved in 42.5% of patients. Another phase II study is currently assessing the efficacy of the combination of gemcitabine and sunitinib in sarcomatoid RCC (Clinical Trials. gov NCT0056049). We are very interested in these studies and we hope to further investigate such chemo-switch, multi-targeted approaches in patients with mRCC.

In our case, we used gemcitabine before sunitinib and observed that gemcitabine and sunitinib hold great treatment potential against mRCC individually. The new drugs (TKIs, mTOR inhibitors and others) are a major advantage. On the other hand, old classical chemotherapeutic agents should not be forgotten because they too may become a treatment option in selected patients for mRCC.

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