Remarkable shrinkage of sarcomatoid renal cell carcinoma with single-agent gemcitabine

Yoshiro Fujiwara[a], Katsuyuki Kiura[a,b], Masahiro Tabata[b], Nagio Takigawa[b], Katsuyuki Hotta[a], Shigeki Umemura[a], Masako Omori[c], Kenichi Gemba[d], Hiroshi Ueoka[e] and Mitsune Tanimoto[a,b]

A 60-year-old Japanese man presented to our hospital with a painful left hip. Computed tomography showed a tumor in the left kidney and metastases in the left gluteus maximus muscle and lung. The pathological diagnosis of a biopsy specimen obtained from a metastatic lesion in the left gluteus maximus muscle was sarcomatoid renal cell carcinoma. On admission, his general condition was extremely poor. He was confined to bed because of severe left hip pain and confusion, possibly caused by hypercalcemia. This seriously ill patient suffering from advanced sarcomatoid renal cell carcinoma was treated with single-agent gemcitabine, resulting in symptom relief and a dramatic improvement in his status; all of the tumors had regressed significantly by the 11th dose of gemcitabine. These findings indicate that single-agent gemcitabine is one of the few chemotherapeutic agents effective for palliation in patients with sarcomatoid renal cell carcinoma, even those with poor performance status. *Anti-Cancer Drugs* **19:431–433 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Departments of [b]Respiratory Medicine, [c]Pathology, Okayama University Hospital, [d]Department of Respiratory Medicine, Japan Labor Health and Welfare Organization Okayama Rosai Hospital, Okayama and [e]Department of Respiratory Medicine, National Hospital Organization Sanyo Hospital, Ube, Japan

Correspondence to Dr Katsuyuki Kiura, MD, PhD, Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558, Japan
Tel: +81 86 235 7227; fax: +81 86 232 8226;
e-mail: kkiura@md.okayama-u.ac.jp

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Introduction

Sarcomatoid renal cell carcinoma (SRCC), a pathologic variant of renal cell carcinoma (RCC) containing both carcinomatous and sarcomatous components, is a rare tumor of the kidney that constitutes 1–8% of all renal neoplasms [1]. The prognosis of SRCC is extremely poor because of its aggressive behavior and resistance to treatment [2]. Whereas immunotherapy is the standard treatment for patients with advanced RCC, it appears to be ineffective for those with advanced SRCC. To date, the optimal treatment for advanced SRCC remains undetermined.

Gemcitabine is a pyrimidine nucleoside antimetabolite that has shown modest antitumor activity for a wide variety of solid tumors, including pancreatic, breast, bladder, and non-small-cell lung cancer. In contrast, gemcitabine has only limited activity against RCC, with a response rate of 6–8% [3,4]. Gemcitabine, however, remains a promising drug, because it is not a known substrate for P-glycoprotein [5], which is considered to be the major cause of chemoresistance in RCC. In addition, gemcitabine has some activity against soft tissue sarcoma [6]. Accordingly, of the various chemotherapeutic agents available, gemcitabine may offer the best chance of a response in patients with SRCC. Regarding its toxicity, gemcitabine can also be given to patients safely, even those with a poor performance status (PS), because myelosuppression is the main toxicity of gemcitabine, and its nonhematological toxic effects are relatively mild [7].

This report describes a seriously ill patient with advanced SRCC, who responded to gemcitabine monotherapy, which resulted in symptom relief and a dramatic improvement in his PS.

Case report

A 60-year-old Japanese man complaining of left hip pain was referred to us in May 2004. On admission, his general condition was extremely poor. He was confined to bed because of severe left hip pain and confusion, possibly caused by hypercalcemia. A hard mass was palpable in his left hip. Laboratory examination showed leukocytosis (white blood cell count 50 600/mm^3: 84% neutrophils, 7% lymphocytes, 7% monocytes, 2% eosinophils) and hypercalcemia (15.3 mg/dl, serum calcium level corrected for albumin). The serum concentration of parathyroid hormone-related protein was elevated to 4.1 pmol/l (normal value less than 1.1 pmol/l). The serum level of cytokeratin 19 fragment was also elevated to 11.4 ng/ml (normal value less than 2.8 ng/ml). Computed tomography (CT) of the abdomen demonstrated a huge mass

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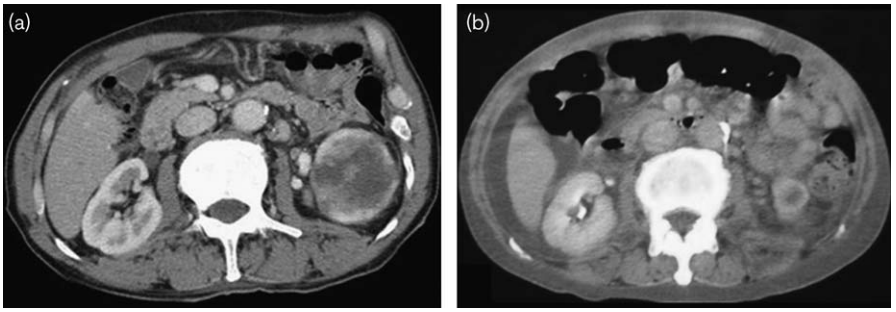
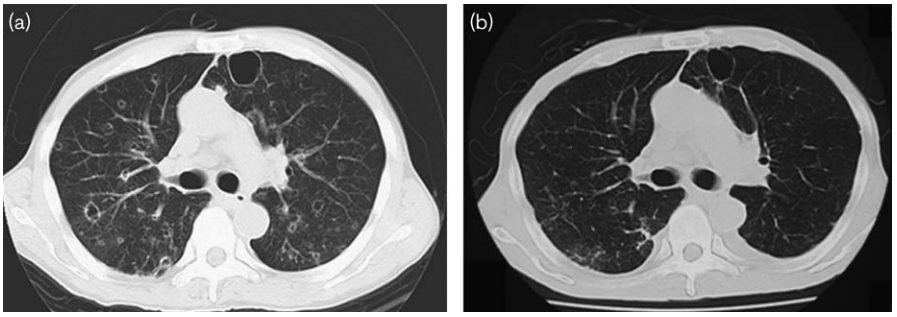
Fig. 1



(a) A huge mass in the lower pole of the left kidney (60 × 59 mm) was detected on computed tomography (CT) of the abdomen. (b) After treatment, CT of the abdomen demonstrated marked regression of the primary tumor (22 × 20 mm).

Fig. 2

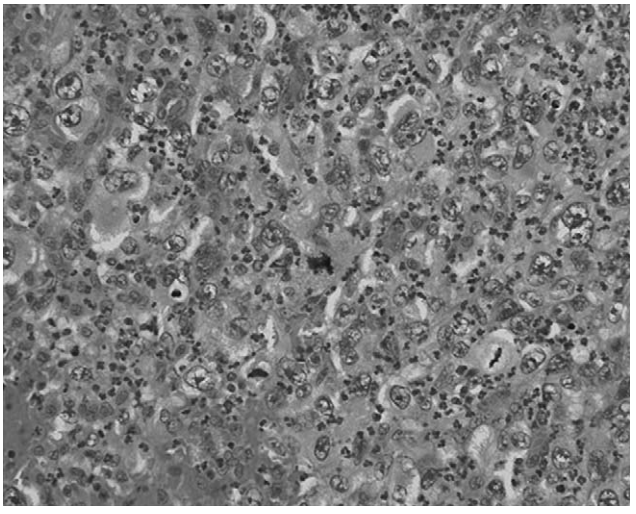


(a) Multiple pulmonary nodules with thin-walled cavities were imaged with computed tomography (CT) of the chest. (b) CT of the chest revealed that the multiple pulmonary metastases had regressed markedly after the chemotherapy.

in the lower pole of the left kidney (60 × 59 mm; Fig. 1a) and a mass in the left gluteus maximus muscle (48 × 30 mm). CT of the chest revealed multiple pulmonary nodules with thin-walled cavities (Fig. 2a). Bone scintigraphy and brain magnetic resonance imaging revealed no metastatic lesion. The biopsy specimen of the left hip mass showed both sarcomatous components consisting of pleomorphic spindle cells and giant cells and carcinomatous components composed of clear epithelial cells (Fig. 3). Immunohistochemistry showed diffuse positive staining of the tumor cells for cytokeratin and vimentin, whereas calretinin, S-100, desmin, and CD34 staining were negative. CD10, a glycoprotein expressed on the brush border of renal tubular cells [8], also stained positive, strongly supporting a renal epithelial origin of the tumor. Ultimately, the patient was diagnosed as having SRCC with metastases in the left gluteus maximus muscle and lung.

In May 2004, gemcitabine was initiated as a 30-min intravenous infusion at a dose of 650 mg/m^2, which was repeated once weekly. His consciousness level and left

Fig. 3



Both pleomorphic spindle cells and giant cells resembling sarcoma and clear epithelial cells compatible with renal clear cell carcinoma were observed (hematoxylin and eosin stain; original magnification, × 100).

hip pain rapidly improved, and his elevated white blood cell count and serum calcium level subsequently normalized. His serum cytokeratin 19 fragment decreased to 4.2 ng/ml in July 2004. The primary tumor (22×20 mm; Fig. 1b) and metastatic lesion in the left gluteus maximus muscle (24×20 mm) had regressed markedly on CT after 11 cycles of gemcitabine. The multiple cavitary pulmonary metastases had also nearly disappeared (Fig. 2b). Toxicity was generally mild and well tolerated. The patient's PS, according to the Eastern Cooperative Oncology Group scale, improved from 4 to 0. In August 2004, he was discharged without any symptoms. After resistance to the treatment developed, he, however, died because of the rapid progression of SRCC at a local hospital 2 months later.

Discussion

We experienced an extraordinary case of a SRCC patient achieving a remarkable shrinkage after the weekly administration of gemcitabine. Single-agent gemcitabine was given to a seriously ill patient safely, and provided clinical benefit, including symptom relief and a dramatic improvement in the patient's PS.

Although the role of chemotherapy in advanced SRCC is not well established, some cases seem to benefit from chemotherapy. Culine *et al.* [9] reported four partial responses to combination chemotherapy, mainly a doxorubicin-containing regimen. Sella *et al.* reported complete responses in two patients using cyclophosphamide, vincristine, doxorubicin, and dacarbazine [10]. These aggressive chemotherapy regimens are, however, usually associated with major toxic effects, and they are not only applicable to a limited number of patients but also unlikely to be suitable for patients with a poor PS. Clinically, gemcitabine has been shown to be a feasible treatment for patients with a poor PS [11]. Our case suggests that single-agent gemcitabine is a safe and effective treatment for palliation in patients with advanced SRCC, even those having a poor PS.

Molecular targeted agents such as sunitinib and sorafenib have recently shown a survival benefit in patients with metastatic RCC [12,13]. This suggests that these antiangiogenic agents might also be effective for advanced SRCC. Further evaluation is needed to assess the efficacy and safety of antiangiogenic agents in patients with advanced SRCC, including a poor PS, in the future, because the trials included only patients with clear cell carcinoma and a good PS.

This case is unique in several aspects. First, the patient had leukocytosis and hypercalcemia, which are well-known indicators of paraneoplastic syndrome [14]. Despite a lack of strong evidence, the patient's white blood cell count and serum calcium level paralleled the tumor progression and normalized following chemotherapy, suggesting that these abnormalities were attributable to the tumor. Second, a skeletal muscle metastasis, which is an uncommon site of distant metastasis [15], was confirmed in our patient pathologically. Third, multiple cavitary pulmonary metastases, which are an infrequent form of pulmonary metastasis [16], were observed. These phenomena may reflect the aggressiveness of the tumor in this case. Although all of the tumors initially responded to gemcitabine monotherapy, they relapsed within a short interval and progressed rapidly.

In conclusion, we presented a seriously ill patient with advanced SRCC, who responded to gemcitabine monotherapy. Further investigation is warranted to evaluate the value of gemcitabine monotherapy as a therapeutic option in patients with advanced SRCC, especially those with a poor PS.

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