Biochemical and Pathological Response of Prostate Cancer in a Patient with Metastatic Renal Cell Carcinoma on Sunitinib Treatment

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Sunitinib is a small molecular inhibitor of tyrosine kinases and is used to treat advanced renal cell carcinoma and gastrointestinal stromal tumour after disease progression or intolerance to imatinib therapy. Here, we describe biochemical and pathological response of prostate cancer in a patient with metastatic renal cell carcinoma during sunitinib treatment. A 62-year-old man was referred to our hospital because of a mass in the scalp. He was diagnosed with left renal cell carcinoma with right renal and scalp metastases. In addition, synchronous prostate cancer involving less than one-half of the right lobe was found with a prostate-specific antigen (PSA) value of 23.4 ng/ml. Treatment was begun with sunitinib (50 mg daily, 4 weeks on and 2 weeks off). Regarding the prostate cancer, active monitoring was planned considering the far advanced renal cell carcinoma. Surprisingly, the PSA level was 3.4 ng/ml at week 6 and 0.2 ng/ml at week 12, and it subsequently remained normal. At the time of writing (cycle 6 of sunitinib therapy), the prostate nodule significantly decreased in size. Furthermore, a 12-core re-biopsy revealed pathological evidence of regression with sunitinib treatment, with control of his renal cell carcinoma.

Key words: prostate cancer − sunitinib − treatment outcome

INTRODUCTION

Sunitinib is an oral small molecular inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-KIT), and has received approval from US FDA and European Agency for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumour after disease progression or intolerance to imatinib therapy. In addition, sunitinib has also demonstrated evidence of activity in other solid tumours (1). We describe our case of biochemical and pathological response of prostate cancer in a patient with metastatic renal cell carcinoma on sunitinib treatment, and we discuss the possible mechanism underlying the effects of sunitinib on prostate cancer.

CASE REPORT

In March 2008, a 62-year-old man was referred to our hospital because of a mass in the scalp that showed poorly differentiated carcinoma with diffuse infiltrative growth, cellular pleomorphism and abundant clear cytoplasm on biopsy (Fig. 1). The patient had been well until 3 months before admission, when he noticed the scalp mass and developed abdominal discomfort with weight loss. Examination revealed an erythematous scalp mass in the left parietal area and costovertebral angle tenderness on the left side. The laboratory results were normal, except for an increased prostate-specific antigen (PSA) of 23.4 ng/ml (reference 0−2.5 ng/ml), which had been checked for screening purposes considering his age. The digital rectal examination revealed a palpable lesion involving less than one-half of the right lobe of the prostate (cT2a). Transrectal ultrasound showed a hypo-echogenic nodule in the right lobe (Fig. 2a). An adenocarcinoma was diagnosed after transrectal biopsy, with a

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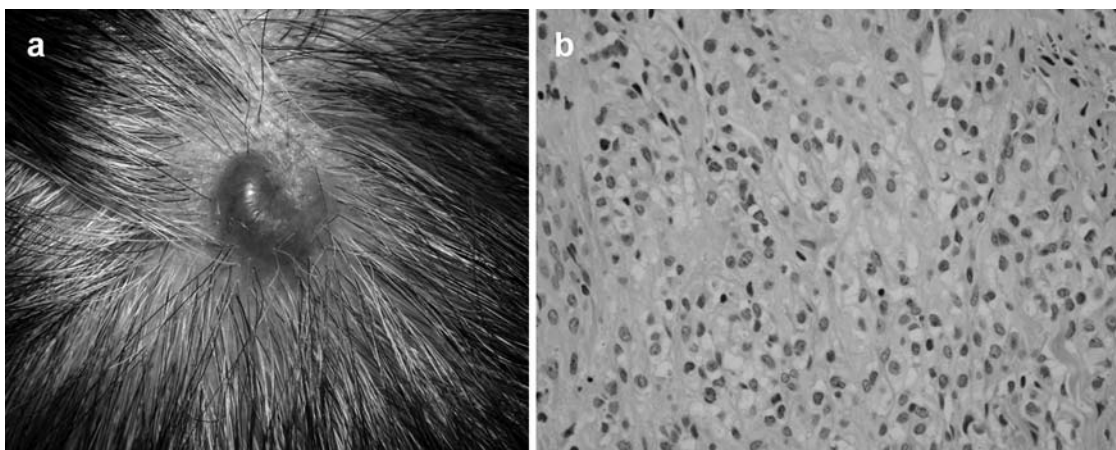
Figure 1. (a) An erythematous scalp mass in the left parietal area. (b) Microscopic view of the scalp mass showing clear cell morphology (haematoxylin and eosin, ×400). A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.
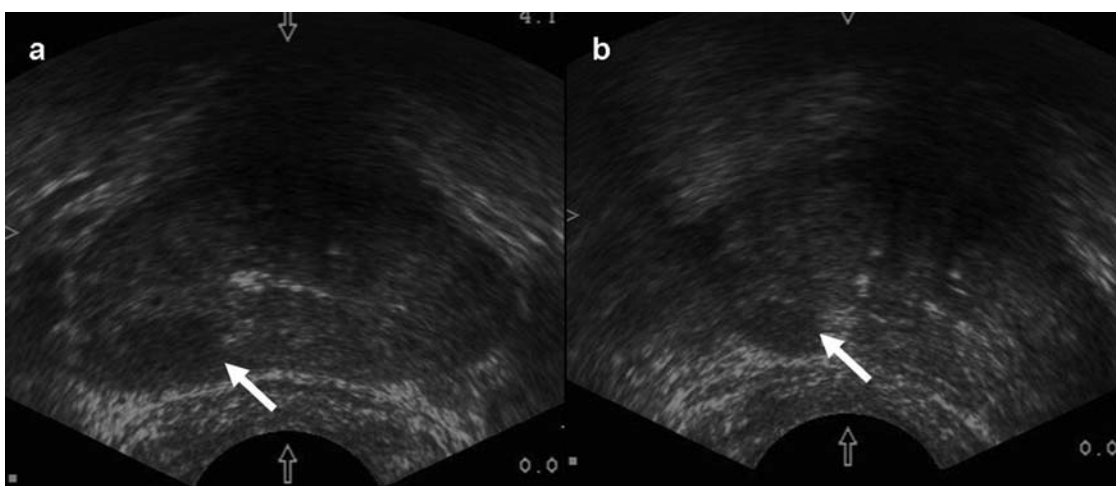

Figure 2. Transrectal ultrasound demonstrates a hypo-echogenic nodule (white arrow) in the right lobe of the prostate. (a) Before sunitinib treatment and (b) after sunitinib treatment.

Gleason score of $4 + 4 = 8$. Computed tomography (CT) of the abdomen revealed an 8.2×4.9 cm mass in the left kidney, which had invaded beyond Gerota's fascia. Another mass, 1.7 cm in diameter, was present in the left adrenal gland. There were multiple small nodular lesions in the right kidney. Considering the pathological feature of the scalp mass and the abdominal CT findings, a diagnosis of left renal cell carcinoma with left adrenal, right renal and scalp metastases was made. He was placed in the intermediate risk group using the Memorial Sloan-Kettering Cancer Center (MSKCC) risk stratification model. Treatment was begun with sunitinib (50 mg daily, 4 weeks on and 2 weeks off). Regarding the prostate cancer, active monitoring was planned considering the far advanced renal cell carcinoma. He tolerated the sunitinib with manageable adverse events. Surprisingly, the PSA level was 3.4 ng/ml at week 6 and 0.2 ng/ml at week 12, and it subsequently remained normal. At the time of writing (cycle 6 of sunitinib therapy without reduction and interruption of dose), the prostate nodule significantly decreased in size as determined by digital rectal examination and transrectal ultrasound (Fig. 2b). Furthermore, a 12-core re-biopsy revealed pathological evidence of regression (Fig. 3) with sunitinib treatment, with partial response of his renal cell carcinoma (Fig. 4).

DISCUSSION

To our knowledge, this is the first published report of localized prostate cancer showing biochemical and pathological response with sunitinib treatment. Sunitinib has shown anti-angiogenic and anti-tumour activities in various solid xeno-graft models (1–3). In addition, sunitinib has recently been used to treat advanced renal cell carcinoma and gastrointestinal stromal tumours after disease progression or intolerance to imatinib therapy (4,5). Regarding the role of sunitinib in the treatment of prostate cancer, sunitinib alone or in combination with docetaxel inhibits the growth of
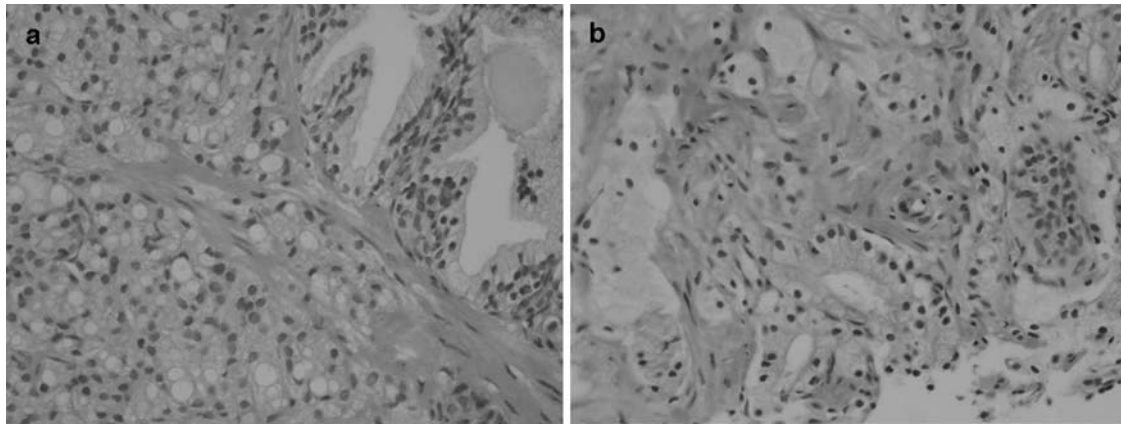
Figure 3. Section of the prostate biopsy before (a) and after (b) sunitinib treatment, respectively. (a) The tumour tissue consists of fused, ill-defined glands with poorly formed glandular lumina and signet-ring cell features. The nuclei of tumour cells are well demarcated and hyperchromatic. (b) The tumour tissue shows focal loss of glandular pattern with myxoid degeneration. The nuclei of some tumour cells show pyknosis and loss of nuclei (necrosis) (haematoxylin and eosin, ×400). A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.
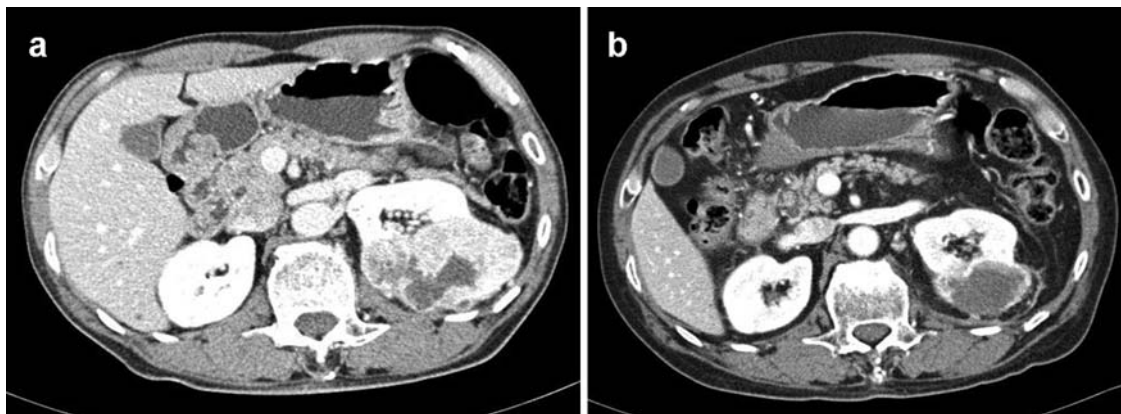

Figure 4. Computed tomography of abdomen before (a) and after (b) sunitinib treatment showed marked tumour shrinkage and necrosis.

hormone-refractory prostate cancer cell xenografts (6,7). Furthermore, sunitinib in combination with docetaxel and prednisone showed promising preliminary efficacy with a response rate of 33% in patients with hormone-refractory prostate cancer and an overall PSA response rate of 55% (8), and sunitinib monotherapy showed modest clinical benefit in both chemonaive and docetaxel-resistant patients with castration-resistant prostate cancer (9). In addition, two Phase II trials of sorafenib, which is another oral multikinase inhibitor, showed the possibility of clinical benefit in patients with androgen-independent prostate cancer (10,11).

At present, there are no data in the literature on the *in vivo* use of sunitinib for androgen-dependent prostate cancer. Hormone-dependent prostate cancer patients are usually treated with surgery, radiation or hormonal therapy based on the extent of disease. However, the widespread use of each of these approaches has increased the short- and long-term adverse consequences with varying morbidity and mortality. The adverse effects of radical prostatectomy include immediate post-operative complications and long-term urinary and sexual complications, and radiation therapy in men with

localized prostate cancer may lead to urinary, gastrointestinal and sexual complications, although improvements in surgical and radiation techniques have reduced the incidence of these complications. Hormone treatment, usually androgen-deprivation therapy, induces bone density loss and fracture, diabetes and cardiovascular disease. Therefore, various clinical trials have addressed strategies to prevent treatment-related side effects and improve the quality of life for men with prostate cancer (12,13). In view of these points, the biochemical and pathological response of localized prostate cancer with sunitinib treatment with manageable toxicity in our patient suggests a role for sunitinib in the treatment of androgen-dependent prostate cancer, although the mechanism underlying the effects of sunitinib on prostate cancers remains to be clarified. Various signalling pathways may be involved; the expression of PDGF and activation of the PDGFR are associated with the growth of prostate cancer cells, and there is strong evidence that VEGF is involved in the development of prostate cancer (14,15). In addition, VEGF levels are elevated and higher levels are associated with increased mortality in prostate cancer patients (16–18).

In vitro experiments have shown that imatinib inhibits tumour growth and angiogenesis by blocking the effects mediated by PDGF and VEGF (14,15). Furthermore, c-KIT and PDGFR are expressed in the testis and involved in testosterone production, and are inhibited by imatinib (19). Therefore, the possibility of a hormonal mechanism in the regression of prostate cancer cannot be excluded. We speculate that similar effects of sunitinib may induce the regression of prostate cancer in our patient, although further trials would be warranted to evaluate these potential benefits.

In conclusion, in our patient, sunitinib might have exerted its anti-tumour activity by inhibiting various signalling pathways and, possibly, through hormonal manipulation with favourable toxicities, suggesting its role in the treatment of androgen-dependent prostate cancer.

Conflict of interest statement

None declared.

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