Safety and efficacy of sunitinib in advanced renal cell carcinoma (RCC)

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Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney[1]. It is associated with a poor prognosis and high specific mortality; 5-year survival rates in the USA vary from 90.8% for localized disease to 11.0% for distant metastatic disease[2]. According to the Institut National de Santé Publique (INSP) Algiers Cancer Registry, the incidence of RCC in Algeria is 3.7/100,000 for males and 2.2/100,000 for females[3].

Immunotherapy, with interleukin (IL)-2 and/or interferon (IFN)-a, has been widely used to treat RCC for a number of years[4–6]. However, these cytokines have limited efficacy in the majority of patients (5–20% response rates)[4–6]. Growing understanding of the pathogenesis of RCC has led to the identification of factors associated with disease development, including the connection between inactivation of the von Hippel–Lindau (VHL) gene and clear-cell RCC. VHL gene alterations are associated with increased production of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF), and overexpression of these growth factors may promote tumor angiogenesis and subsequent tumor enlargement[7]. The emergence of novel targeted therapies has provided several new treatment options with greater efficacy compared with cytokines[7]. Sunitinib is a small-molecule tyrosine-kinase inhibitor (TKI) that inhibits cellular signaling via multiple targets including PDGF and VEGF receptors[8]. It has shown efficacy in Phase ll and lll clinical trials in metastatic RCC (mRCC)[9–12] and is recommended as a first-line treatment option and considered a reference standard of care for the first-line treatment of patients with advanced and/or metastatic RCC[13,14].

This study assessed the safety and efficacy (overall survival [OS], progression-free survival [PFS], and objective response rate [ORR]) of sunitinib in Algerian patients with advanced RCC.

Patients and methods

Seventy-four patients with advanced RCC were enrolled between January 2007 and December 2010. Of these, all but one had undergone prior nephrectomy. Patients received sunitinib (50 mg/day) in 6-week cycles, consisting of 4 weeks of treatment followed by 2 weeks without treatment. Treatment continued until disease progression or the occurrence of intolerable adverse events. Radiologic and clinical assessments were performed at baseline and at regular intervals to evaluate treatment response.

Results

Baseline characteristics including assessment of sites of metastases, tumor histology, Eastern Cooperative Oncology Group (ECOG) performance scores and Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification are shown in Table 1.

Tumor response could be assessed in 59 patients. Of these, a partial response was seen in 15 (25.4%), while 27 (45.7%) had stable disease (stable for >3 months in 20 [33.9%]; Table 2). At 18 months, 70% (52 of 74) of the patients were alive and the median PFS was 10 months (range 8–16 months; Table 2). Examples of patient responses following sunitinib treatment can be seen in the CT scans in Figures 1 and 2.

Of the six patients with locally advanced RCC, five underwent nephrectomy, pancreatic and splenic resection. At the end of the study, all five were still alive. Two are free of disease progression after 36 months and 38 months, while the remaining three relapsed after 19, 20 and 22 months, respectively (Table 3).
Seven patients received sorafenib as second-line therapy, in six cases because of relapse and in one case due to intolerance of sunitinib. Prolonged response was observed in one patient and stable disease in two patients.

Sunitinib was generally well tolerated and the adverse events observed were those typically associated with sunitinib treatment. One patient with a history of hypertension died due to cardiac toxicity (Grade 3) and one patient experienced Grade 3 dysarthria. Eight patients experienced Grade 3 abdominal pain and on endoscopy were found to have peptic ulcers. Other Grade 3 events observed included nausea, abdominal pain, stomatitis and hand–foot syndrome. Grade 3 neutropenia (1 patient), thrombopenia (2) and anemia (3) were also observed. No Grade 4 toxicity was observed.

Discussion

The efficacy of sunitinib in mRCC has been confirmed in both Phase II and III trials[9–12]; in the Phase III trial the ORR, median PFS and OS rates were all higher compared with interferon-alpha (IFN-α)[9,10]. Moreover, sunitinib treatment was associated with better quality of life[15, 16].

The present report describes the safety and efficacy of sunitinib in patients with advanced RCC and is one of the largest series reported from a single center in Algeria. At 18 months, 70% (52/74) of the patients enrolled in the study were alive, with 46% (N=34) having stable disease. The median PFS of 10 months was consistent with the PFS of 11.0 months observed in the Phase III trial[10]. Thus, sunitinib demonstrated significant efficacy, and also proved to have an acceptable safety profile, with adverse events similar to those seen in other studies. Therefore, the use of sunitinib for the treatment of advanced RCC appears to be a safe and effective treatment option in the Algerian patient population.

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Tables

Table 1. Baseline characteristics of patients

Characteristic	Sunitinib (N=74)
Median age (years)	56
Prior nephrectomy, n (%)	73 (98.6)
Patients with metastases, n (%)	68 (92)
Patients with multiple sites of metastases, n (%)	22 (32.3)
Bone + lung	9
Lung + peripheral lymph nodes	3
Breast + peritoneum	1
Liver + peritoneum	3
Bone + lung + brain	2
Bone + lung + lymph nodes	1
Liver + lung	3
Patients with locally advanced disease, n (%)	6 (8)
ECOG performance status, n (%)	
0	52 (70.2)
1	18 (24.3)
2	4 (5.4)
Tumor histology, n (%)	
Clear cell	66 (89.1)
Papillary	4 (5.4)
Carcinoma + sarcoma	4 (5.4)
MSKCC risk classification, n (%)	
Good (0 risk factors)	24 (32.4)
Intermediate (1–2 risk factors)	45 (60.8)
Poor (≥3 risk factors)	5 (6.8)

ECOG PS 0 = Asymptomatic; ECOG PS 1 = Symptomatic but completely ambulatory; ECOG PS 2 = Symptomatic, in bed <50% of day

Table 2. Tumor responses to sunitinib (by RECIST criteria) in 59 evaluable patients

	n (%)
Partial response	15 (25.4)
Stable disease	27 (45.7)
Stable disease (>3 months)	20 (33.9)

Table 3. Progression-free survival of patients with locally advanced RCC

Patients with locally advanced RCC	Months progression free
Patient 1	38+
Patient 2	36+
Patient 3	22
Patient 4	20
Patient 5	19

Figures

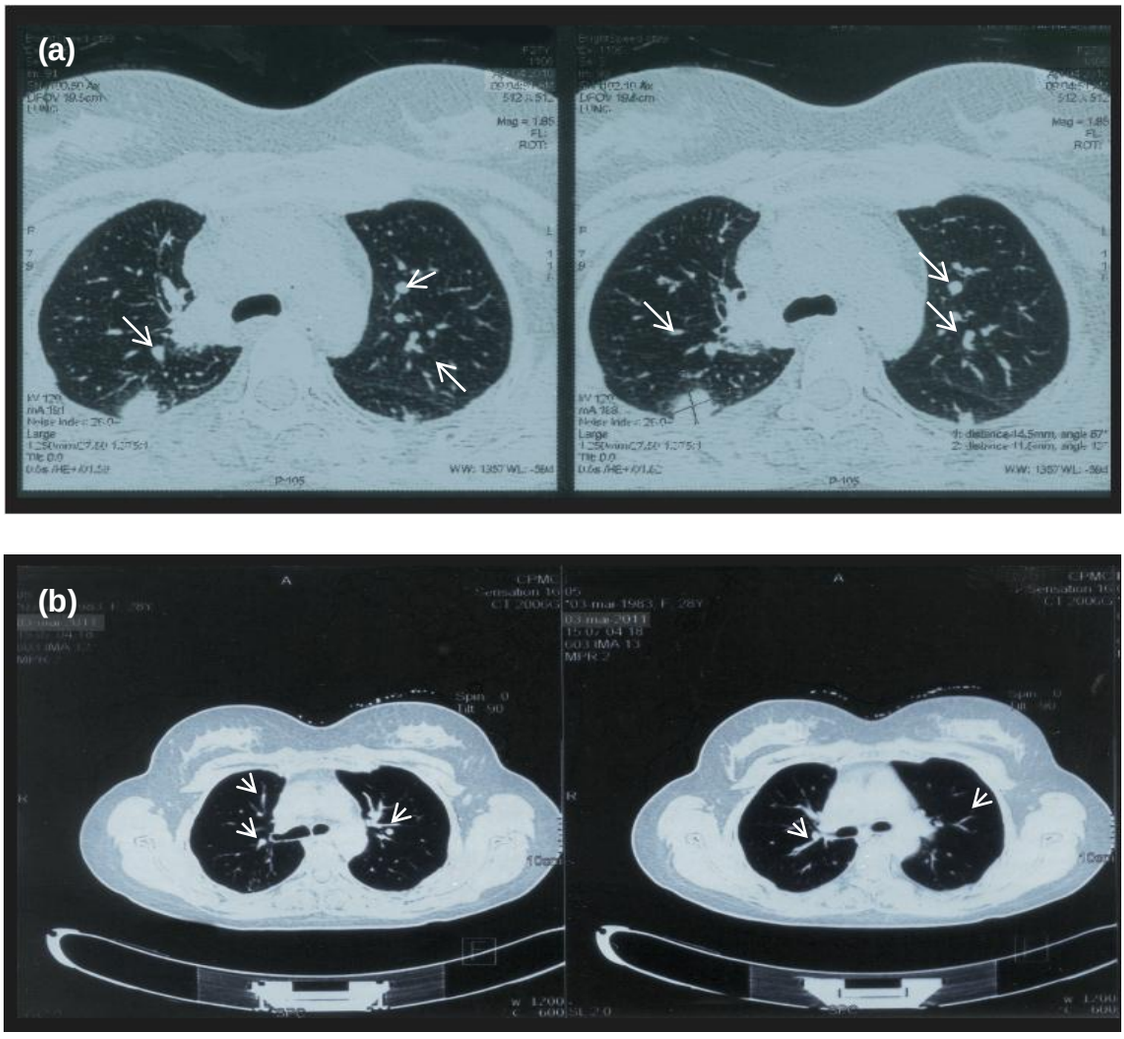

Fig1: (a) Initial CT scan (April 2010) showing metastatic RCC nodules (white arrows) in lungs of a patient; (b) CT scan following sunitinib treatment (March 2012) showing tumor response and remaining nodules (white arrows)

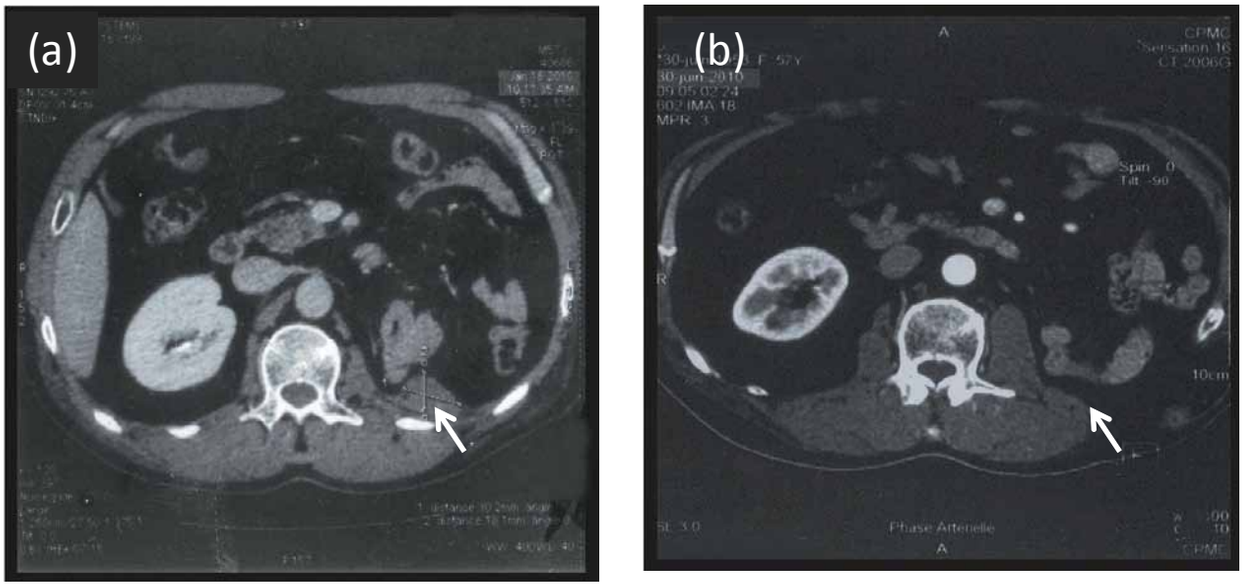

Fig2: (a) Initial CT scan showing site of nephrectomy to remove a RCC (January 2010; some tumor unresectable because of adhesions); (b) CT scan following sunitinib treatment (June 2010) showing tumor disappearance