Original Study

A Phase II Trial of Sunitinib in Patients With Renal Cell Cancer and Untreated Brain Metastases

Christine Chevreau,[1] Alain Ravaud,[2] Bernard Escudier,[3] Eric Amela,[4] Remy Delva,[5] Frederic Rolland,[6] Diego Tosi,[7] Stephane Oudard,[8] Ellen Blanc,[9] Celine Ferlay,[9] Sylvie Négrier[9,10], for the French Group on Renal Cancer

Abstract

In this prospective trial, the efficacy and safety of sunitinib in patients with previously untreated brain metastases (BM) in metastatic renal cell cancer (RCC) were evaluated. Safety appears to be acceptable, however, its efficacy is limited, with no objective response and poor median overall survival.

Background: The expanded access program and anecdotal cases suggested sunitinib is safe in RCC patients with BM and might have worthwhile activity. **Patients and Methods:** In a phase II trial, patients with untreated BM received the standard regimen of sunitinib. The primary end point was objective response (OR) rate in BM after 2 cycles. An OR rate of 35% was prospectively defined as the minimum needed to warrant further investigation. According to Simon's optimal 2-stage design, at least 3 of the initial 15 patients had to have an OR for accrual to continue. **Results:** Among 16 evaluable patients, 1 had a complete response outside the central nervous system (CNS). CNS disease was stabilized in 5 (31%). However, no BM showed an OR. Therefore, no further accrual took place. Median time to progression was 2.3 months and overall survival was 6.3 months. There was 1 toxic death, from peritonitis with gastric perforation. Three patients experienced at least 1 treatment-related grade 3 or greater toxicity but no neurological adverse events were attributable to sunitinib. **Conclusion:** Although tolerability was acceptable in RCC patients with previously untreated BM, sunitinib has limited efficacy in this setting.

Clinical Genitourinary Cancer, Vol. 12, No. 1, 50-4
Keywords: Brain metastases, Clinical trial, Renal cell carcinoma, Sunitinib

Introduction

Although there is wide variation in the reported incidence of brain metastases (BM) in patients with renal cell cancer (RCC), with figures ranging from 4% to 48% cited, central nervous system (CNS) involvement is undoubtedly frequent[1] and in a recent European registry, RCC was second only to lung cancer as a source of cerebral metastases. In a series of more than 11,000 metastatic RCC (mRCC) patients from the Nationwide Inpatient Sample (NIS) in the United States, the rate of BM in patients with exclusively abdominal metastases was 2%, but that in patients with thoracic and bone metastases was 16%.[2] In the overall NIS population, 8% of patients were affected. The effective detection of BM and—if surgical and radiotherapy options are exhausted—effective systemic management is a major unmet medical need.

Sunitinib (Sutent, Laboratoire Pfizer) is an oral tyrosine kinase inhibitor (TKI) which selectively blocks certain proangiogenic growth factors involved in mRCC. Among its targets are the vascular endothelial growth factor receptor (VEGFR) types 1-3, and the platelet derived growth factor receptor-α and -β. Sunitinib has proven efficacy in the first-line treatment of patients with metastatic clear-cell RCC, having been shown to more than double median progression-free survival (PFS) when compared with interferon alfa in the pivotal phase III trial.[3] Sunitinib remains a standard of care in this setting.[4]

The TKI sorafenib is also a VEGFR inhibitor. As with sunitinib, sorafenib is a small molecule with a wide distribution in tissues including the CNS. In the pivotal phase III trial of sorafenib in mRCC, patients randomized to sorafenib were less likely to develop BM (3%) than those in the placebo arm (12%).[5] However, in the

[1]Institut Claudius Regaud, Toulouse, France
[2]Centre Hospitalier Universitaire Saint André, Bordeaux, France
[3]Institut Gustave Roussy, Villejuif, France
[4]Centre Oscar Lambret, Lille, France
[5]Institut de Cancérologie de l'Ouest, Angers, France
[6]Institut de Cancérologie de l'Ouest, Saint Herblain, France
[7]Institut regional de Cancérologie de Montpellier, Montpellier, France
[8]Hôpital Européen Georges Pompidou, University Paris Descarte, Paris, France
[9]Centre Leon Bérard, Lyon, France
[10]Université Lyon, Lyon, France

Submitted: Jun 6, 2013; Revised: Sep 12, 2013; Accepted: Sep 24, 2013; Epub: Sep 28, 2013

Address for correspondence: Christine Chevreau, MD, Medical Oncology Department, Institut Claudius Regaud, 20-24, rue du Pont Saint-Pierre, 31052 Toulouse cedex, France
E-mail contact: chevreau.christine@claudiusregaud.fr

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2013.09.008

sorafenib expanded access program, among the 47 patients with BM evaluable for efficacy, a partial response was seen in only 2 (4%).[6]

Considering their poor prognosis, patients with known BM were excluded from the pivotal trial of sunitinib in RCC.[3] In the expanded access program, in contrast, 321 patients known to have had CNS lesions at baseline were included and received a median of 3 cycles of treatment.[7] Thirty-two percent of these patients with BM discontinued for lack of efficacy, and 8% because of adverse events. However, sunitinib appeared to be safe in patients with asymptomatic or previously treated BM; and cases of tumour regression were reported. Twelve percent of the 213 evaluable patients had an objective response. Median PFS was 5.6 months and median overall survival (OS) 9.2 months. Complete response in an mRCC patient with BM has also been described.[8]

Based on these retrospective data, sunitinib has been suggested as a good therapeutic option for RCC patients with BM. However, in the conclusion to their report on BM patients in the expanded access program, Gore et al recommended that the potential activity of sunitinib in this setting should be studied prospectively.[7] It was, therefore, appropriate to carry out this controlled, prospective phase II study to assess the potential activity of sunitinib against CNS metastases from RCC.

Patients and Methods

Patients

Male and female patients aged 18 years or older with measurable (more than 2 cm) and inoperable BM from renal adenocarcinoma of any histology were eligible for this multicenter phase II study. Cytological or histological confirmation of RCC, including Fuhrman grade, was mandatory. To be enrolled, patients had to have an Eastern Cooperative Oncology Group Performance Status of 2 or less and adequate organ function. They had not previously been exposed to sunitinib (at least not within the 6 months before study entry) and had not been treated for BM. Patients had to be asymptomatic or have symptoms adequately controlled with steroid treatment for at least 2 weeks. Exclusion criteria included cerebral metastasis presenting as hemorrhage, presence of an isolated BM of less than 2 cm amenable to surgery or radiosurgery, previous treatment with growth factors, and uncontrolled hypertension.

The study was approved by local Institutional Review Boards. All patients were fully informed and gave written consent.

Study Treatment

Sunitinib was administered orally at 50 mg daily for 4 weeks followed by 2 weeks of no drug use (ie, according to a 6-week cycle). Treatment continued until either disease progression or intolerable toxicity. In individual patients, the dose was reduced to 37.5 mg or 25 mg daily when required by the nature and severity of toxicity. No other anticancer treatment was allowed for the duration of the patients' participation in the study.

End Points

The main objective of the study was to determine the objective response rate (ORR), including complete and partial responses, in cerebral metastases after 2 cycles of sunitinib, ie, 10-12 weeks after the start of treatment. Secondary end points were response duration, ORR for lesions outside of the CNS, disease stabilization, time to progression (TTP), PFS, OS, the course of tumor-related neurological symptoms, and overall tolerability of treatment. A further objective was to determine whether any factors predictive of response could be identified at initial assessment or in the first 2 weeks of therapy.

Brain metastases were assessed using magnetic resonance imaging (MRI) every 2 cycles and response classified according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria by a central review committee. Response duration was calculated from the date of first response until the occurrence of documented progression or death. TTP was calculated as the time from inclusion in the study until progression or death from progressive RCC, and censored at the date of last assessment or death from a cause other than cancer. PFS was calculated as the time from inclusion until the date of first evidence of progression or death or date of last assessment. OS was calculated as the time from date of inclusion until death from any cause or last follow-up. The course of symptomatic neurological symptoms was assessed according to the use of corticosteroids.

Toxicity was graded according to the National Cancer Institute-Common Terminology Criteria classification (version v3.0). Particular attention was paid to the possible risk of acute, treatment-related neurological toxicities of grade 3 or greater severity, the exacerbation of existing neurological deficits, the appearance of new signs that were not rapidly reversible, or the need to increase the dose of corticosteroids. Neurological toxicity was judged in relation to the frequency of such events expected on the basis of our clinical experience. Patients

Table 1 Patient Characteristics

Characteristic	Value
Median Age, Years	62
Sex, Male	13 (75)
More Than 1 Metastatic Site	10 (59)
Previous Nephrectomy	7 (41)
Clear-Cell Carcinoma	16 (94)
ECOG PS 0-1	14 (88)[a]
MSKCC Intermediate or Poor Risk	10 (77)[b]
Corticosteroid Therapy	12 (75)
Median Number of CNS Metastases (Range)	1 (1-4)
Median Sum of Diameters (Range), mm	23 (10-61)

Data are presented as n (%) except where otherwise noted. n = 17 patients.
Abbreviations: CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MSKCC = Memorial Sloan-Kettering Cancer Center.
[a]One missing value.
[b]Four missing values.

Table 2 Best Response According to RECIST Criteria

Site	Best Response	n
Brain	SD	5
Other Sites[a]	CR	1[b]
	SD	5[c]

Abbreviation: RECIST = Response Evaluation Criteria In Solid Tumors.
[a]The other sites were: pulmonary metastases (12 patients), liver metastases (2 patients), bone (5 patients), kidney (1 patient), abdominal lymph node (3 patients), adrenal gland (4 patients), mediastinum (8 patients), pleura (1 patient), skin (1 patient), and others (2 patients).
[b]Cutaneous metastases.
[c]Pulmonary metastases, bone, kidney, adrenal gland, and abdominal lymph nodes.