Sarcomatoid Renal Cell Carcinoma: Clinical Outcome and Survival After Treatment With Sunitinib

Victoria Kunene,[1] Manuela Miscoria,[2] Sarah Pirrie,[3] Mohammad R. Islam,[4] Mehran Afshar,[1] Emilio Porfiri[1,3]

Abstract

We retrospectively reviewed the clinical outcomes of 23 patients with advanced sarcomatoid renal cell carcinoma treated with sunitinib. Median overall survival was 15.7 months, progression-free survival 5.7 months, and response rate 30%. Patients with good performance status had 20.9 months median survival whereas patients with poor performance status had 5.0 months. The percentage of sarcomatoid component did not influence outcomes.

Background: Renal tumors with sarcomatoid changes are aggressive malignancies with poor prognosis. Immunotherapy and chemotherapy have provided little benefit. The efficacy of treatments targeting the vascular endothelial growth factor pathway is unclear because of the lack of clinical trial data and the small number of published series. **Patients and Methods:** We reviewed the clinical records of 23 consecutive patients with advanced sarcomatoid renal cell carcinoma who were treated with sunitinib in our center. Overall survival (OS), progression-free survival, and response rate were evaluated. We also studied the effect on clinical outcome of performance status, prognostic risk group, and proportion of sarcomatoid component. **Results:** Median OS was 15.7 months (95% confidence interval [CI], 5.0-21.2). Median progression-free survival was 5.7 months (95% CI, 3.2-12.6). Seven patients (30%) had an objective response, 5 patients (22%) had stable disease, and 11 (48%) had progressive disease. The median survival of the 13 (56.5%) patients with performance status of 0 to 1 was 20.9 months (95% CI, 9.7-63.3) whereas the medial survival of the 10 (43.5%) patients with performance status of 2 to 3 was 5.0 months (95% CI, 1.1-16.5). Objective responses were observed only among the 13 (56.5%) patients with performance status of 0 to 1. Heng prognostic risk group and percentage of sarcomatoid component did not influence outcome. **Conclusion:** Sunitinib shows efficacy in advanced renal tumors with sarcomatoid differentiation particularly in patients with good performance status. Appropriate patient selection and risk-directed treatment remains essential in this aggressive disease.

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Introduction

Sarcomatoid differentiation represents a histological variant found in 5% to 8% of all renal cell carcinomas (RCCs). These tumors are aggressive malignancies with poor prognosis and a high risk of relapse after surgery.[1-3] Patients with sarcomatoid RCC often present with advanced disease and low performance status (PS), their management being challenging because of the rarity of the sarcomatoid variant and the lack of convincing clinical trial data. Although some responses were initially observed with interleukin 2 or doxorubicin treatment, the results of the trials using immunotherapy or chemotherapy have been disappointing.[4-10] The advent of drugs targeting the vascular endothelial growth factor (VEGF) pathway or the mammalian target of rapamycin pathway has revolutionized the management and improved the prognosis of RCC.[11] Unfortunately, patients with sarcomatoid tumors were excluded from most clinical trials of targeted drugs[12-14] and in other trials the percentage of patients with sarcomatoid component was not reported.[15,16] Therefore, the efficacy of targeted drugs has not been assessed in this malignancy and

[1]Cancer Centre, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom
[2]Azienda Ospedaliero - Universitaria Ospedali Riuniti Trieste, Dipartimento di Oncologia - Ospedale Maggiore, Trieste, Italy
[3]Cancer Research Clinical Trial Unit, School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom
[4]Department of Medicine, The Royal Marsden Hospital, London, United Kingdom

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Address for correspondence: Dr Emilio Porfiri, MD PhD, Cancer Centre, Queen Elizabeth Hospital, Birmingham, Edgbaston, Birmingham B15 2WB, United Kingdom
Fax: +44 (0)121-371-3590; e-mail contact: e.porfiri@bham.ac.uk

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the data currently available derive from small retrospective series. There are no specific guidelines for the management of patients with sarcomatoid RCC: they are commonly treated with VEGF-targeted therapies, in fewer instances with chemotherapy or simply referred for supportive care. Molina and colleagues reviewed the outcomes of 63 patients who were treated with cytokines or VEGF-targeted therapies, mainly sunitinib, in the past 11 years.[17] The median survival of the 29 patients who were treated with sunitinib was 10 months and the progression-free survival (PFS) was 4.4 months. Four (14%) of the 29 patients achieved a partial response (PR). Golshayan and colleagues examined a series of 43 patients with sarcomatoid RCC who were treated with VEGF-targeted therapies.[18] The 21 patients treated with sunitinib showed a survival of 11.8 months and a PFS of 5.3 months. Six patients (28%) achieved a PR: these patients had tumors showing a sarcomatoid component which represented < 20% of the neoplastic tissue. Patients treated with sorafenib or bevacizumab achieved similar outcomes. In another series, 9 patients in whom chemotherapy had failed were treated with sorafenib and achieved 1 objective response and 3 disease stabilizations.[9] We retrospectively reviewed the outcomes of all patients with sarcomatoid RCC who were treated with sunitinib at our center. The effect of clinical and pathological prognostic factors was evaluated.

Patients and Methods

Patients

The medical records of 23 consecutive patients with sarcomatoid RCC who commenced treatment with sunitinib at Queen Elizabeth Hospital Birmingham, UK, between June 2006 and April 2010 were reviewed. Baseline patient characteristic data were collected. Histological subtype and percentage of sarcomatoid elements were recorded. The percentage of sarcomatoid elements was quantified as part of the routine diagnostic process for all but 1 patient for whom a review of the histology specimen was carried out. The study was authorized by the Institutional Review Board of the Queen Elizabeth Hospital Birmingham.

Treatment

Sunitinib was administered using the standard '4 weeks on-2 weeks off' schedule and patients were reviewed every 3 to 6 weeks. Dose reductions and dose interruptions were carried out by the attending physician according to the type and grade of the toxicity observed. Treatment was discontinued in case of radiological or clinical evidence of tumour progression or in case of unacceptable toxicity.

Outcome Data and Statistical Analysis

The primary clinical outcome was overall survival (OS), calculated from the start of the treatment with sunitinib to death from any cause and patients were censored at the date they were last known to be alive. Secondary clinical outcomes were PFS, and response rate. PFS was measured from the start of treatment to disease progression or death from any cause and patients were censored at the date they were last known to be progression-free and alive. Estimates of OS and PFS were calculated using the Kaplan-Meier method, hence the limited number of patients must be recognized when considering these results. Tumor response was assessed using computed tomography scans repeated every 3 courses or earlier if clinically indicated. Tumor response was quantified using the Response Evaluating Criteria in Solid Tumors and classified as: complete response (CR), PR, stable disease (SD), or progressive disease (PD). Median follow-up and its confidence interval (CI) was estimated using the Kaplan-Meier method with reverse censoring. Patients were stratified according to Eastern Cooperative Oncology Group PS, Heng prognostic model,[19] and percentage of sarcomatoid component. Patients with a PS of 0 to 1 and PS of 2 to 3 were grouped for the analysis because the number was too small to subdivide them into individual PS groups. The cutoff PS of 0 to 1 versus PS of 2 to 3 was chosen because in most cases only patients with PS $\leq$ 1 are eligible for clinical trials and the same cutoff was thought to be useful for comparative purposes. Fisher exact test was used to compare response rates based on PS, Heng classification, and percentage sarcomatoid component. The 4 categories (CR, PR, SD, PD) were treated separately in the Fisher exact test analysis as performed by Golshayan and colleagues.[18]

Results

Patients

The median age was 59 years, 21 patients (91%) had had a nephrectomy either radical or cytoreductive, 5 patients (21%) had previous immunotherapy (Table1). The median percentage of the

Table 1 Patient Characteristics

Characteristic	Value
Patients (Male/Female), n	23 (15/8)
Median Age (Range), Years	59 (32-78)
Previous Nephrectomy	21 (91%)
Previous Immunotherapy, n (%)	
Interferon alpha	4 (17)
Interleukin 2	1 (4)
Median Time From Diagnosis to Starting Sunitinib (Range), Months	8 (2-54)
Histology, n (%)	
Clear cell	18 (78)
Chromophobe	1 (5)
RCC unclassified	4 (17)
Percentage of Sarcomatoid Component	
Median	30% (range, 5%-95%)
Sarcomatoid component ≤20%, n (%)	9 (39)
Sarcomatoid component >20%, n (%)	14 (61)
ECOG Performance Status, n (%)	
0-1	13 (56.5)
2-3	10 (43.5)
Number of Metastatic Sites, n (%)	
1	5 (22)
2	5 (22)
>2	13 (56)
Patients With Brain Metastases, n (%)	4 (17)
Heng Risk Stratification, n (%)	
Favorable risk	1 (4)
Intermediate risk	11 (48)
Poor risk	11 (48)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RCC unclassified = renal cell carcinoma not otherwise specified.