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Efficacy and toxicity of sunitinib in patients with metastatic renal cell carcinoma with renal insufficiency

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Abstract ***Background:*** Patients with metastatic renal cell carcinoma (mRCC) with renal insufficiency are generally excluded from clinical trials, despite their increasing numbers. Thus, we evaluated the efficacy and toxicity of sunitinib in such patients.
Patients and methods: Korean patients with mRCC with renal insufficiency who had received sunitinib as first-line treatment between January 2008 and May 2012 were included. Patient characteristics, clinical outcomes and toxicities were evaluated. Overall survival (OS) and progression-free survival (PFS) were determined according to the degree of renal impairment.
Results: The median age of the 34 patients evaluated was 66 years, 90% had an Eastern Cooperative Oncology Group performance status of 0 or 1 and the median glomerular filtration rate was 46.5 mL min^{-1}·1.73 m^{-2} (range, 21.1–59.5). The starting sunitinib dose was 37.5

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and 50 mg for 12 and 22 patients, respectively. A 4-weeks-on–2-weeks-off regimen was followed for 31 patients; a 2-weeks-on–2-weeks-off regimen, for one patient; and a daily regimen, for two patients. The best response was partial response in eight patients and stable disease in 12. Median OS and PFS times were 26.3 months (95% confidence interval [CI]: 17.1–35.3) and 12.2 months (95% CI: 10.2–13.2), respectively. Common non-haematologic adverse events (AEs) were stomatitis, rash, general oedema and fatigue. The most common AEs of ⩾grade 3 severity were fatigue, neutropenia and thrombocytopenia.

Conclusions: In patients with mRCC with renal insufficiency, sunitinib was efficacious and did not cause increased toxicity. Thus, clinicians should not hesitate to treat patients with mRCC with renal insufficiency with sunitinib.

1. Introduction

Over the past several years, treatment options for metastatic renal cell carcinoma (mRCC) have dramatically increased with the development of various targeted agents that inhibit elements of the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin pathways [1–5]. Sunitinib, a multi-targeted tyrosine kinase inhibitor of the VEGF receptor, platelet-derived growth factor receptor, and c-kit showed a significant antitumour effect over interferon alpha in a phase III trial [6]. Worldwide, sunitinib is approved for the initial standard treatment of mRCC in patients with an intermediate to good prognosis.

Globally, the incidence and mortality rates of renal cell carcinoma (RCC) have increased making it one of the most lethal cancers [7–9]. The prevalence of RCC is higher among patients with end-stage renal disease (ESRD) and recipients of kidney transplants than in the general population, and these patients have distinct clinical and pathological RCC features [8,10,11]. The incidence of RCC is also higher in patients with chronic kidney disease than in the general population, and a significant number of these patients show progression to ESRD, with or without nephrectomy [8,12,13]. With the developments in modern medical treatment and the resulting increase in life span, the number of patients with renal insufficiency has increased, as has the prevalence of chronic co-morbidities associated with renal insufficiency, such as cancer [10,11,14,15].

Patients with renal insufficiency are generally excluded from pivotal clinical trials. In previous studies of sunitinib, patients with serum creatinine concentrations of ⩾1.5 times or >2.0 times the upper limit of normal were excluded [6,16]. However, the number of patients with mRCC with renal insufficiency is increasing and a standard protocol for their treatment should be developed. Case reports and several studies have described the efficacy and toxicity of sunitinib in patients with mRCC with renal insufficiency [17–21]. Several studies have reported that the pharmacokinetics of sunitinib in these patients is similar to that in patients with mRCC with normal renal function [22,23].

The aim of this retrospective study was to evaluate the efficacy and toxicity of sunitinib in Korean patients with mRCC with chronic renal insufficiency not requiring dialysis.

2. Patients and methods

The Korean Renal Cell Cancer Registry (KRCCR, http://kcsg-rcc.or.kr) was searched to identify patients with mRCC with chronic renal insufficiency not requiring dialysis who received sunitinib as first-line treatment between January 2008 and May 2012. The Cockcroft-Gault formula was used to calculate the glomerular filtration rate (GFR). Patients with a GFR of $\geqslant 15$ mL min^{-1} · 1.73 m^{-2} but <60 mL min^{-1} · 1.73 m^{-2} were eligible for assessment. Patients were divided into two groups according to the degree of renal insufficiency as defined by the National Kidney Foundation [24]: moderate renal impairment (30 mL min^{-1} · 1.73 m^{-2} $\leqslant$ GFR $<$ 60 mL min^{-1} · 1.73 m^{-2}) and severe renal impairment (15 mL min^{-1} · 1.73 m^{-2} $\leqslant$ GFR $<$ 30 mL min^{-1} · 1.73 m^{2}). The following clinical data were retrospectively obtained: demographics (age, gender), Eastern Cooperative Oncology Group (ECOG) performance status, stage at diagnosis, prognostic risk group based on the Memorial Sloane Kettering Cancer Center Criteria (MSKCC), performance of prior nephrectomy and serum creatinine concentrations. The following data about sunitinib were obtained: initial dose and schedule of sunitinib, serum creatinine concentration during and after the use of sunitinib, dose reductions and adverse events (AEs) and laboratory abnormalities that were graded according to the National Cancer Institute Common Terminology Criteria for AEs version 3.0. Best response as defined by the Response Evaluation Criteria In Solid Tumours, progression-free survival (PFS) and overall survival (OS) data were also collected.

2.1. Statistical analysis

Categorical data are presented as frequency counts and percentages, and continuous variables, as medians