Analysis of adverse events of sunitinib in patients treated for advanced renal cell carcinoma

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Submitted: 12 August 2014
Accepted: 25 November 2014

Arch Med Sci 2016; 12, 2: 360–364
DOI: 10.5114/aoms.2016.59262

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Abstract

Introduction: Treatment of the metastatic stage of renal cell carcinoma is specific because classical chemotherapy is not applicable here. The treatment is mainly based on molecularly targeted drugs, including inhibitors of tyrosine kinases. In many cases the therapy takes many months, and patients often report to general practitioners due to adverse events. In this article, the effectiveness and side effects of one of these drugs are presented. The aim of the study was to analyse of the toxicity and safety of treatment with sunitinib malate in patients with clear cell renal cell carcinoma in the metastatic stage.
Material and methods: Adverse events were analyzed using retrospective analysis of data collected in a group of 39 patients treated in the Department of Systemic and Generalized Malignancies in the Cancer Center in Krakow, Poland.
Results: Toxicity of treatment affected 50% of patients. The most common side effects observed were hypertension, thrombocytopenia, stomatitis, diarrhea and weakness. Grade 3 serious adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 4 affected up to 10% of patients. The most common serious adverse events were hypertension and fatigue.
Conclusions: Sunitinib malate is characterized by a particular type of toxicity. Knowledge of the types and range of adverse events of this drug is an important part of oncological and internal medicine care.

Key words: sunitinib, renal cell carcinoma, adverse events, treatment time to progression, toxicity of treatment.

Introduction

Kidney cancer accounts for 2–3% of all malignant tumors. Eighty percent of cases occur after the age of 40, and the incidence rate for men compared with women is 3 : 2; in 2009 the National Cancer Registry recorded 2,733 cases among men and 1,866 cases among women [1].

Kidney cancer is often asymptomatic, resulting in late diagnosis. More than half of tumors are detected incidentally in imaging studies. The rest cause discrete symptoms such as fatigue, low-grade fever, and recurrent inflammation of the urinary tract. The classic triad of symptoms (Virchow's triad) – hematuria, flank pain and a palpable tumor – occurs in 6–10% of patients [2].

The World Health Organization (WHO) classifies kidney cancer according to its pathomorphology [3].

Staging and prognosis

The clinical stage of kidney cancer was determined by TNM classification (7th edition, 2010) [4]. The prognosis was determined according to the Motzer scale of the Memorial Sloan Kettering Cancer Center (MSKCC), which was created by Motzer *et al.* to determine the survival prognosis of patients. Today, it is also used to select an appropriate therapy [5].

Nephrectomy or kidney-sparing surgery should be considered for each patient. In the early stages of the disease, it allows recovery and in metastatic kidney cancer it prolongs survival [6, 7].

Systemic treatment

Molecularly targeted drugs and interferon alpha are used today in the treatment of kidney cancer. Patients with a good prognosis according to the MSKCC scale, after nephrectomy and with metastases in the lungs only, are qualified for immunotherapy with interferon.

Sunitinib malate is a small molecule inhibitor of multiple receptor tyrosine kinases, including platelet-derived growth factor receptors α and β, vascular endothelial growth factor (type 1, 2 and 3), Fms-like tyrosine kinase 3 receptor, stem cell factor receptors, glial cell line-derived neurotrophic factor receptors, and colony-stimulating factor receptors.

In 2009, the results of a third phase trial were published; its aim was to compare the efficacy of interferon α and sunitinib as first-line treatment of patients with clear cell renal cell carcinoma with metastases. In the group of patients treated with sunitinib, 47% of patients achieved an objective response to treatment; in the group treated with interferon α, an objective response was achieved in 12% of patients. Median progression-free survival (PFS) was 11 months for sunitinib and 5 months for interferon α. Median overall survival (OS) was 26.7 months for sunitinib and 23.7 months for interferon α. Twenty percent of patients receiving sunitinib and 23% of patients treated with interferon α discontinued the treatment because of adverse reactions [8].

The National Comprehensive Cancer Network, the National Cancer Institute and the Polish Union of Oncology recommend using sunitinib in the first-line treatment of patients with favorable and intermediate prognosis (0–2 risk factors according to the Motzer scale) for metastatic renal cell carcinoma [9–12].

Standard dosing of sunitinib is 50 mg/day for 4 weeks, and then it is stopped for 2 weeks.

Material and methods

We analyzed the data of 39 patients with a diagnosis of clear cell renal cell carcinoma treated with sunitinib malate at the Cancer Center in Krakow, Poland, between 2007 and 2012. In all patients, the disease was at the metastatic stage.

Results

Table I presents the classification of patients due to predictors, according to the MSKCC scale. 51.3% (20 patients) were male and 48.7% (19) were female. The average age at diagnosis of metastatic disease was 62.6 years (range: 41–81 years). Table II presents the classification of patients by site of the metastases.

The median time from diagnosis of renal cell carcinoma to metastasis was 18.1 months. All patients underwent nephrectomy before receiving sunitinib.

In 30 (77%) patients, metastases were observed in more than one place. None of the patients had metastases in the central nervous system.

Twenty-three patients stopped therapy because of: disease progression in 14 patients, adverse events in 8 patients, 1 patient was lost to follow-up.

The occurrence of adverse events was analyzed using information from the physical examination as well as laboratory tests and imaging.

The median follow-up was 31.3 months (range: 17.3–32.6 months). The median duration of treatment was 6.3 months (range: 0.97–23.2 months).

Evaluation of the first response to treatment revealed: 1 (2.6%) patient – total remission, 15 (38.5%) patients – partial remission, 14 (35.9%)

Table I. Classification of patients according to the Motzer scale

Number of factors	Number of patients	Percentage of patients
0	16	41.0
1	11	28.2
2	9	23.1
3	3	7.7

Table II. Patients by site of metastases

Site of metastasis	Number of patients	Percentage of patients
Lungs	26	66.7
Lymph nodes	19	48.7
Liver	9	23.1
Soft tissues	24	61.5
Bones	11	28.2

Table III. Adverse events of all grades during treatment (according to CTCAE 4.0) [12]

Adverse event	Number of patients	Percentage of patients
Thrombocytopenia	13	33.3
Hypertension	17	43.6
Pulmonary embolism	0	0
Deep vein thrombosis	2	5.1
Bleeding	3	7.7
Neutropenia	15	38.5
Fatigue	13	33.3
Diarrhea	2	5.1
Stomatitis	13	33.3
Swelling of the eyelids	6	15.4
Vomiting	4	10.3
HFSR (hand-foot skin reaction)	5	12.8
Yellowing of the skin	4	10.3
Anemia	1	2.6
Other (nausea, increase in liver enzymes, itching of the skin, headache)	6	15.4

Table IV. Serious adverse events (Grades 3–4) during treatment (according to CTCAE 4.0) [12]

Adverse event	Number of patients	Percentage of all patients
Thrombocytopenia	1	2.6
Hypertension	4	10.3
Neutropenia	3	7.7
Fatigue	4	10.3
Stomatitis	2	5.1
Increase in liver enzymes	1	2.6

patients – stabilization of disease, 6 (15.4%) patients – progression, 3 (7.7%) patients – no evaluation; 1 patient was lost to follow-up, 2 patients discontinued treatment because of adverse events, and imaging studies were postponed until resolution of symptoms.

Discussion

Based on the analysis, the most common adverse events were hypertension, neutropenia, thrombocytopenia, fatigue, and stomatitis (Table III). Adverse events that appeared during treatment did not reach the Grade 4 according to CTCAE 4, and grade 3 events affected up to 10% of patients (Table IV). We did not record pulmonary embolism or bleeding from the tumors.

Eight (20.5%) patients did not receive further treatment because of the following adverse events: hypertension in 2 cases, stomatitis in 1, hand-foot syndrome in another 1, asthenia in 2 patients, vomiting in 1 and exacerbation of neurological symptoms (see below). All these adverse events were classified as Grade 3 toxicity and were resistant to symptomatic treatment.

In Motzer *et al.*'s study, therapy was discontinued in 19% of patients because of adverse effects and in Gore *et al.*'s study 8% of patients discontinued [8, 13].

In 1 patient, further treatment was discontinued because of an exacerbation of neurological symptoms (tetraparesis), and in the statistical analysis the patient was assigned to the group that discontinued treatment because of adverse events. We do not associate these symptoms with sunitinib administration, however, as they appeared prior to treatment. The patient was diagnosed with cervical spinal stenosis.

All patients with previously diagnosed arterial hypertensive disease had to have normal blood pressure at the time of initiation of sunitinib. Arterial hypertension as an adverse event of sunitinib was defined as an increase in blood pressure above the normal range, the necessity of increasing doses of hypertensive drugs or the necessity of adding another drug. Grade 3 hypertension occurred in 4 (10.3%) patients whereas Motzer *et al.* [8] found it in 12%, and Gore *et al.* [13] in 5%. According to Rini *et al.*, this symptom is associated with a better response rate, and longer PFS and OS [14]. Physiologically, vascular endothelial growth factor (VEGF) plays a role in blood pressure regulation by its influence on vasorelaxation or vasodilation. This process is regulated by nitric oxide [15]. Inhibition of VEGF by sunitinib leads to vasoconstriction as a result of reduced bioavailability of nitric oxide. There is also a suggestion that hypertension is a result of reduced renal excretion of sodium and water, reduced endothelial function and an elevated level of endothelin-1 [16, 17].

In 2 of 4 patients with grade 3 hypertension, treatment was discontinued because of resistant hypertension (uncontrolled disease despite the use of three or more antihypertensive drugs including diuretics). In these cases blood pressure returned to a normal level after stopping sunitinib but continuation of antihypertensive drugs was necessary.

In the other 2 patients, treatment continued because pharmacological equalization of the ele-

vated blood pressure was achieved and the sunitinib dose was reduced to 25 mg/day. Normalization of blood pressure was possible by using combinations of drugs with different mechanisms of action. In these cases it was necessary to use ACE inhibitors (or sartans), β-blockers, diuretics and a calcium channel blocker.

Grade 3 thrombocytopenia occurred in 1 (2.6%) patient; in the literature, this symptom was observed slightly more frequently: 6–9%, according to data from Motzer *et al.*, Gore *et al.* and others [8, 13, 18–22].

Grade 3 neutropenia occurred in 3 (7.7%) patients; in other studies, the frequency was 8–13% [8, 13, 18, 19, 21–23].

Hematologic toxicity may be a result of inhibition of receptors expressed on hematopoietic stem cells (KIT, PDGFR, FLT3) [24].

There are reports that the occurrence of neutropenia or/and thrombocytopenia is connected with prolonging time to progression, overall survival and progression-free survival [25].

High-grade fatigue affected 4 (10.3%) patients; in other studies, this high-grade adverse event occurred with a frequency of 7–10% [13, 18, 19, 21].

According to data from published studies, weakness during sunitinib treatment is often a symptom of hypothyroidism [26]. According to data provided by Kollmannsberger *et al.* [21] and Eisen *et al.* [27], in 85% of patients treated with sunitinib, the values of any studied thyroid hormone are incorrect, but clinical signs of hypothyroidism are not always apparent. Originally, we did not determine the level of thyroid-stimulating hormone (TSH); thus, it is difficult to assess in how many patients weakness was caused by the treatment and in how many by reduced levels of free thyroid hormones. Currently, the TSH level is routinely determined for each patient starting treatment.

High-grade stomatitis affected 2 (5.1%) patients; in data from other authors, this percentage was 1–5% [18, 19].

In the treated patients, 8 (20.5%) required dose reduction to 25 mg/day because of adverse events: 2 had hypertension, 2 had increased liver enzyme levels, and the following events occurred one each in a single patient: stomatitis, weakness, neutropenia, and anemia. In each of these patients, the adverse event resolved sufficiently to allow continued therapy.

Adverse events of grade lower than Grade 3 resolved spontaneously or with symptomatic treatment. None led to the interruption of treatment (for example treatment of arterial hypertension according to guidelines [28]).

In conclusion, in the analyzed group of 39 patients, sunitinib malate treatment was effective in prolonging survival time and time to disease progression. The toxicity associated with treatment that was observed in this group is comparable with the data reported by other authors. The experience with this drug allows better prophylaxis and treatment of side effects.

Conflict of interest

The authors declare no conflict of interest.

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