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Adverse drug reactions associated with sunitinib therapy: characteristics and risk factors

Neželjena dejstva sunitiniba: karakteristike i faktori rizika

Snežana Mugoša*†, Zoran Džamić‡, Majda Šahman-Zaimović*†, Nevenka Lukovac-Janjić§

University of Montenegro, *Faculty of Medicine, §Institute for Oncology and Radiotherapy, Podgorica, Montenegro; †Institute for Medicines and Medical Devices, Podgorica, Montenegro; ‡University of Belgrade, Faculty of Medicine, Clinic for Urology, Belgrade, Serbia

Abstract

Background/Aim. Kidney tumors account for 2–3% of all tumors. Renal cell carcinoma (RCC) is the tenth most common malignancy. Sunitinib is used as the first treatment line in patients with a good and intermediate prognosis. The aim of this study was to analyze the risk factors, frequency, and adverse drug reactions (ADRs) of sunitinib in patients with metastatic RCC. **Methods.** The retrospective study included 170 patients treated at the Clinic for Oncology of the Clinical Center of Montenegro, Urology Clinic of the Clinical Center of Serbia, and Clinic for Oncology of the Clinical Center Niš. As a data source, we used patient medical histories and/or electronic patient records. ADRs were characterized by using Rawlins and Thompson classification. Each ADRs severity was assessed in accordance with the World Health Organization criteria. Causality was assessed using the Naranjo probability scale. **Results.** ADRs of sunitinib occurred in 152 (89.4%) patients. ADRs were 89% type A and 11% type C. Disorders of the blood and lymphatic system, gastrointestinal disorders, and disorders of the skin and subcutaneous tissue were the most common manifestations of ADRs of sunitinib. Causality assessment was most commonly classified as certain (60%). Serious ADRs occurred in 4.5% of patients. Most patients recovered without consequences. The most common manifestations of ADRs were: leukopenia, hypothyroidism, thrombocytopenia, diarrhea, stomatitis, asthenia, and hypertension. All ADRs were expected. The number of concomitant medications and the duration of therapy proved to be the most significant risk factors for ADR to sunitinib. **Conclusion.** Our study shows that the incidence of ADRs of sunitinib in patients with kidney cancer is high. The ADRs were mostly moderate and mild in intensity and occurred as a consequence of the pharmacological action of the drug. It is necessary to conduct continuous education of medical oncologists in the field of monitoring safe drug use, as well as patients on sunitinib therapy, in order to improve their awareness of the sunitinib ADRs and the risk factors that lead to them, with the aim of reducing their frequency.

Key words:
drug-related side effects and adverse reactions; kidney neoplasms; sunitinib.

Apstrakt

Uvod/Cilj. Tumori bubrega čine 2–3% svih tumora. Karcinom bubrežnih ćelija nalazi se na desetom mestu najčešćih maligniteta. Kao prva terapijska linija kod bolesnika sa dobrom i intermedijarnom prognozom koristi se sunitinib. Cilj rada bio je analiza faktora rizika, učestalosti ispoljavljivanja i karakteristika neželjenih dejstava sunitiniba kod bolesnika sa metastatskim karcinomom bubrega. **Metode.** Retrospektivnom studijom je bilo obuhvaćeno 170 bolesnika lečenih na Klinici za onkologiju Kliničkog centra Crne Gore, Urološkoj klinici Kliničkog centra Srbije i Klinici za onkologiju Kliničkog centra Niš. Kao izvor podataka koristili smo istorije bolesti i/ili elektronske kartone bolesnika. Neželjena dejstva su klasifikovana prema *Rawlins and Thompson* klasifikaciji, težina prema kriterijumima Svetske zdravstvene organizacije, a uzročno-posledična povezanost korišćenjem Naranjo skale. **Rezultati.** Neželjena dejstva sunitiniba ispoljila su se kod 152 bolesnika (89,4%). Neželjena dejstva tipa A ispoljila su se kod 89%, a tipa C kod 11% bolesnika. Najčešće su se ispoljili poremećaji krvi i limfnog sistema, gastrointestinalni poremećaji i poremećaji kože i potkožnog tkiva. Uzročno-posledična povezanost između leka i neželjenog dejstva najčešće je klasifikovana kao sigurna (60%). Značajna neželjena dejstva imalo je 4,5% bolesnika. Većina bolesnika se oporavila bez posledica. Najčešća neželjena dejstva bila su: leukopenija, hipotireoza, trombocitopenija, dijareja, stomatitis, astenija i hipertenzija. Sva zabeležena neželjena dejstva bila su očekivana. Najznačajniji faktori rizika od

Correspondence to: Snežana Mugoša, Institute for Medicines and Medical Devices of Montenegro, Bulevar Ivana Crnojevica 64A, 81 000 Podgorica, Montenegro. Email: snezana.mugosa@cinmed.me

nastanka neželjenih dejstava sunitiniba bila su broj istovremeno korišćenih lekova i trajanje terapije. **Zaključak.** Naše istraživanje pokazuje da je učestalost neželjenih dejstava sunitiniba kod bolesnika sa karcinomom bubrega visoka. Neželjena dejstva su uglavnom bila umerena i laka po intenzitetu i nastala su kao posledica farmakološkog dejstva leka. Potrebno je sprovesti dodatnu edukaciju medikalnih onkologa iz oblasti praćenja bezbedne primene lekova, a takođe i bolesnika koji su na terapiji sunitinibom, sa ciljem unapređenja njihove informisanosti o neželjenim dejstvima sunitiniba i faktorima rizika koji do njih dovode, kako bi se njihova učestalost smanjila.

Ključne reči:
lekovi, neželjeni efekti i neželjene reakcije; bubreg, neoplazme; sunitinib.

Introduction

A significant increase in the incidence of renal cell carcinoma (RCC) has been observed in the last 50 years, including cancers detected at an early stage of the disease, which is explained by the increasing use and improvement of diagnostic procedures, as well as the increasing impact of the growing presence of risk factors such as smoking, obesity, and hypertension [1]. Sunitinib, an oral multitargeted tyrosine kinase inhibitor, is used as the first-line treatment in patients with a good and intermediate prognosis, while patients with a poor prognosis are treated with temsirolimus. The therapeutic success of this drug depends on the three most important factors: the dosage of the drug, the length of therapy, and the adverse drug reactions (ADRs) that the drugs cause [2]. The most serious adverse reactions (ADRs) associated with sunitinib, some with fatal outcomes, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and hemorrhages [3]. The most common ADRs (≥1/10) of any grade included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders, skin discolouration, and palmar-plantar erythrodysesthesia syndrome. These ADRs are usually expected to decrease during the treatment.

However, there are ADRs that require additional management due to the metabolic pathway of the sunitinib (by cytochrome P450 3A4) and its pharmacological and toxicological characteristics. Furthermore, sunitinib is intended for long-term use. Therefore, it is very important to consider any problems related to ADRs of the drug that could, among other things, be the reason for the inevitable discontinuation of the drug and adversely affect the comfort of patients during treatment.

The aim of this study was to establish the criteria for detection of ADRs of sunitinib, to analyze these ADRs and risk factors for their development in order to provide recommendations for their prevention, and thus to ensure optimal benefit from sunitinib treatment.

Methods

Study design and patients selection

The retrospective study included 170 patients treated at the Clinic for Oncology of the Clinical Center of Montenegro, Urology Clinic of the Clinical Center of Serbia, and Clinic for Oncology of the Clinical Center Niš during the six-month period, from April to October 2018.

Inclusion criteria were the following: patients of both sexes with metastatic RCC treated with sunitinib in first-line therapy, performance status 0–2. Severely ill patients with performance status > 2 were excluded from the study.

As a data source, we used patient medical histories and/or electronic patient records.

At the very beginning of sunitinib therapy, the expected ADRs were explained to patients. Patients usually had check-ups with a medical oncologist at intervals of 15 days and more often if necessary. Each time a medical report was written. The report contained information about the problems reported by a patient, e.g. skin changes, changes in mucous membranes, headache, etc., and also information about other ADRs noted by the medical oncologist, based on available laboratory and other parameters (e.g. thrombocytopenia, leukopenia, hypothyroidism).

Data on the demographic characteristics of patients, underlying disease, therapy, laboratory, and other available data were entered into the computer database.

Definition and classification of ADRs

Definition of ADRs according to the World Health Organization (WHO) was used in this research [4].

ADRs were characterized by using Rawlins and Thompson [5] classification. Each ADR severity was assessed in accordance with the WHO criteria [4]. The causality relationship between the drug and the effect was established using Naranjo's ADR probability scale [6]. ADRs were classified by criteria suggested by Meyboom et al. [7] as type A ("drug actions"), type B ("patients reactions"), and type C ("statistical").

In addition, the level of intervention was attributed, using a four-level scale: Level 1 – no change in the treatment; Level 2 – dose adjustment or drug stop, no additional treatment required; Level 3 – dose adjustment or drug stop, additional treatment required; Level 4 – transfer to intensive care unit [8]. Each ADR was also classified according to the system organ class, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification of ADRs, as recommended by the WHO [9].

Statistical analysis

Data contained in medical histories and patient records, indicating possible ADRs of sunitinib, were entered into a computer database. Descriptive statistical methods (arithmetic mean, median, standard deviation) and methods for testing statistical hypotheses (*t*-test, Mann-Whitney test, χ^2-test, and Fisher's test of exact probability) were used for the analysis of primary data. Statistical hypotheses were tested at the level of statistical significance (alpha level) of 0.05.

Results

The study included 170 respondents who received sunitinib, 97 (57.1%) from Belgrade, 44 (25.9%) from Podgorica, and 29 (17.1%) from Niš.

The mean age of all subjects in the study was 61.8 ± 9.2 years. The youngest respondent was 24 and the oldest 84 years old. Out of all respondents included in the study, 70.6% were male and 29.4% were female.

Adverse drug reactions of sunitinib occurred in 152 (89.4%) patients (Table 1).

Adverse reactions were present in 84.5% of patients from Belgrade, 97.7% from Podgorica, and 93.1% from Niš. There was a statistically significant difference in the frequency of ADRs in relation to the city (accurate probability test; $p = 0.043$).

The total number of ADRs was 467. Table 2 shows the characteristics of sunitinib ADRs.

The most common certain ADRs were haematological toxicity (leukopenia, thrombocytopenia, and anemia), as well as gastrointestinal system disorders (nausea, diarrhea). The most common probable ADRs were general disorders (asthenia, malaise, myalgia) and endocrine system disorders (primarily hypothyroidism). The most common possible ADRs were loss of appetite, hypertension, headache, and epistaxis.

Serious ADRs, which occurred in 4.5% of patients, included severe skin reactions and severe forms of diarrhea. One patient died due to a possible ADR of sunitinib (renal failure characterized as a possible ADR).

Table 1

Demographic and clinical data of the patients included in the study

Data	Patients without ADRs	Patients with ADRs
	n = 18	n = 152
Age (years), mean ± SD	62.0 ± 7.9	62.5 ± 9.3
Sex, n (%)		
male	14 (77.8)	106 (69.7)
female	4 (22.2)	46 (30.3)
Occupation, n (%)		
employed	2 (11.1)	44 (28.94)
unemployed	7 (38.9)	52 (34.2)
retired	9 (50.0)	56 (36.8)
Education level, n (%)		
elementary	7 (63.6)	4 (36.4)
college	87 (66.9)	43 (33.1)
undergraduate	19 (59.4)	13 (40.6)
graduate	18 (69.2)	8 (30.8)
Comorbidities, n (%)		
endocrine system	2 (13.3)	26 (18.1)
central nervous system	0 (0)	4 (2.8)
gastrointestinal system	0 (0)	4 (2.8)
respiratory system	1 (6.7)	2 (1.4)
cardiovascular system	6 (40)	86 (59.3)
Risk factors for RCC, n (%)		
smoking	11 (100)	82 (65.1)
malignancy history	4 (50)	21 (26.3)
abuse of analgesics	0 (0)	0 (0)
chronic kidney disease	1 (5.6)	7 (4.7)
Disease onset, n (%)		
hematuria	4 (36.4)	41 (35)
back pain	3 (27.3)	17 (14.5)
without difficulty, by accident	2 (18.2)	39 (33.3)
other	2 (18.2)	20 (17.1)
Prevalence of metastases, n (%)		
initially metastatic disease	2 (11.1)	38 (25)
more than 2 metastatic sieves	13 (72.2)	102 (67.1)
Number of drugs, mean ± SD	4.9 ± 1.6	2.1 ± 1.1
Duration of therapy (months), mean ± SD	3.9 ± 2.5	7.4 ± 5.4

ADRs – adverse drug reactions; RCC – renal cell carcinoma; SD – standard deviation.

Table 2

Characteristics of detected adverse drug reactions (ADRs) associated with sunitinib

Characteristics of ADRs	ADRs, n (%)
Type	
A	416 (89.1)
B	0 (0.0)
C	51 (10.9)
Causality	
certain	276 (59.1)
probable	84 (18.0)
possible	98 (21.0)
Level of intervention	
level 1 (no change in dose)	416 (89.1)
level 2 (dose changed or drug stopped)	9 (1.9)
level 3 (drug stopped + additional therapy)	39 (8.0)
level 4 (transfer to intensive care unit)	3 (1)
Severity	
serious	21 (4.5)
non serious	446 (95.5)
Outcome	
death	1 (0.2)
recovery with consequences	4 (0.9)
recovery without consequences	462 (98.9)
Reported by	
patient	234 (50.1)
treating physician	233 (49.9)

The most common manifestations of ADRs were: leukopenia (40%), hypothyroidism (34%), thrombocytopenia (31%), diarrhea (20%), stomatitis (17%), asthenia (17%), and hypertension (16%).

Grades 1–2 ADRs were the most frequent. The frequency of grades 3 and 4 toxicities was relatively low (< 10%).

All ADRs were expected (as described in the Summary of Product Characteristics).

Table 3 shows the prevalence of involved organic systems where ADRs occurred, according to the MedDRA classification.

Table 3

Presentation of adverse drug reactions (ADRs) in different organ systems

Organ system disorders	ADRs, n (%)
Disorders of the blood and lymphatic system	123 (26.3)
Nervous system disorders	18 (3.9)
Gastrointestinal disorders	98 (21)
Respiratory. thoracic and mediastinal disorders	11 (2.4)
Musculoskeletal and connective tissue disorders	9 (1.9)
Eye disorders	9 (1.9)
Endocrine disorders	52 (11.1)
Vascular disorders	25 (5.4)
Skin and subcutaneous tissue disorders	61 (13.1)
General disorders and administration site conditions	35 (7.5)
Laboratory tests	24 (5.1)
Other	2 (0.4)
Total	467 (100)

Discussion

The number of studies where the frequency of adverse reactions to sunitinib was monitored and analyzed is scarce. In our study, we have found that the incidence of sunitinib ADRs in patients treated for RCC was 89%. This data shows that the frequency of ADRs in our study was slightly higher compared to the other studies in which the frequency of ADRs of this drug was about 80% [10]. In a study that comprised 1,073 patients receiving sunitinib, the incidence of ADRs was 82.1% [10].

There are several reasons for such a high incidence of sunitinib ADRs: the different incidence of ADRs in literature can be explained by differences in methodology, the definition of ADRs, classification, algorithms for causality assessment of ADRs, etc. [11]; we have included "possible" ADRs in the total frequency of ADRs, unlike, e.g., some authors [12, 13] who listed only “certain” and “probable” ADRs, thus we may have included some false-positive results; all potential ADRs listed in the Summary of Characteristics of sunitinib were checked, all data contained in medical histories and temperature lists were used, including

laboratory findings, X-ray examinations, ECG, etc.; the population of patients with RCC is comprised mainly of elderly patients, with frequent comorbidities. Numerous previous studies have shown that both age and comorbidity affect pharmacokinetics, i.e., resorption, distribution, metabolism, and excretion of drugs from the body, which makes these patients more sensitive to the occurrence of ADRs [14–18]. The population of the patients included in the study generally receive a large number of drugs at the same time, which turned out to be a significant risk factor for the occurrence of ADRs. In a study of 9,000 Italian patients, mostly over the age of 60, Carbonin et al. [19] showed that the incidence of ADRs increased from 1.2% in patients receiving one drug to 10% in those receiving nine drugs, and to about 50% in patients receiving more than 10 drugs.

Numerous studies [20–24] have shown that the female sex is a risk factor for the occurrence of ADRs, although there is no reliable explanation for this in the literature. Some authors believe that lower body weight and surface area and degree of glomerular filtration, as well as higher fat content, are the reason for the higher frequency of ADRs in the female population [25, 26]. In our study, we did not obtain a statistically significantly higher incidence of sunitinib ADRs in female patients.

When it comes to the causality assessment of ADRs, we obtained the highest prevalence of "certain" ADRs in our study, which differs significantly from the data obtained in similar studies [24, 27–29]. In some studies [27, 29], over 50% of the reported adverse reactions were classified as “possible” and less than 10% as “certain”. In contrast, Classen et al. [20] describes 62% of "certain" ADRs and 0.7% of "probable" ADRs. The reason for the high prevalence of "certain" ADRs in our study stems from the definition of "certain" ADRs, which is that the relationship between the drug and the resulting symptoms and/or signs is established with certainty only if identical clinical and/or laboratory finding occurs on re-exposure to a drug (drug rechallenge). Given that the most common adverse reactions were hematological toxicity (leukopenia, thrombocytopenia, and anemia), as well as gastrointestinal system disorders (nausea, diarrhea) and that these adverse reactions recurred in each cycle of chemotherapy, it is clear that they were classified as "certain" ADRs.

ADRs were 89% type A and 11% type C in our study, which was in accordance with the data obtained by Classen et al. [20]. Given the mechanism of occurrence of these types of ADRs, the prevalence we obtained was expected. In some studies, however, type B reactions accounted for one-third of registered ADRs [30, 31]. Adverse reactions observed with intensive monitoring most often manifested as disorders at the level of the blood and lymphatic system, gastrointestinal disorders, skin and subcutaneous tissue disorders, and endocrine disorders, which is in line with the safety profile of sunitinib [3].

In our study, the data showed that 50% of patients themselves notice the ADRs of sunitinib and report it to their medical oncologist, while the remaining 50% of ADRs are recognized by the oncologist. Numerous studies on informing patients about the ADRs of the drug they take say that additional measures are needed to improve patient awareness, with the aim of accomplishing better compliance and reducing the risk of ADRs [32–34].

Many studies have shown that the percentage of preventable ADRs is high and ranges over 50% [35–39]. This can be achieved by the following methods: knowing the pharmacological characteristics of the drug (including pharmacokinetic and pharmacodynamic properties), as well as the profile of ADRs that the drug can cause, understanding drug interactions when using multiple drugs, avoiding prescribing drugs with the same or similar ADRs profile, dosing drug according to age, body weight, and organ function, medical history taking, which includes pharmacological history, systematic monitoring of ADRs, patients full awareness about all potential ADRs, and precautions when using the drug [40].

The main limitation of the study was the small number of patients in the group without ADRs compared to the other group of patients with ADRs, which makes a large difference in the size of the groups. This implies the necessity to continue this research with more patients in order to increase the power of the study.

Conclusion

Our study shows that the incidence of ADRs of sunitinib in patients with kidney cancer is high. All reported ADRs were expected and described in the Summary of Product Characteristics. The ADRs were mostly moderate and mild in intensity and occurred as a consequence of the pharmacological action of the drug. A lower percentage of ADRs occurred as a result of long-term exposure to the drug. It is necessary to conduct continuous education of medical oncologists in the field of the safe use of drugs monitoring, as well as patients on sunitinib therapy, in order to improve their awareness of the ADRs of sunitinib and the risk factors that could lead to ADRs occurrence in order to reduce their frequency.

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