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

Neželjena dejstva sunitiniba: karakteristike i faktori rizika

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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, asthma, 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.
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 medicinskih 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
nijh dovode, kako bi se njihova učestalost smanjila.

Ključne reči: lekovi, neželjeni efekti i neželjene reakcije; hubreg,
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 inter-
mediate 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 ex-
pected 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 as-
sessed 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, χ²-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

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

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

Table 2

<table>
<thead>
<tr>
<th>Characteristics of ADRs associated with sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics of ADRs, n (%)</td>
</tr>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td><strong>Causality</strong></td>
</tr>
<tr>
<td>certain</td>
</tr>
<tr>
<td>probable</td>
</tr>
<tr>
<td>possible</td>
</tr>
<tr>
<td><strong>Level of intervention</strong></td>
</tr>
<tr>
<td>level 1 (no change in dose)</td>
</tr>
<tr>
<td>level 2 (dose changed or drug stopped)</td>
</tr>
<tr>
<td>level 3 (drug stopped + additional therapy)</td>
</tr>
<tr>
<td>level 4 (transfer to intensive care unit)</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
</tr>
<tr>
<td>serious</td>
</tr>
<tr>
<td>non serious</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>recovery with consequences</td>
</tr>
<tr>
<td>recovery without consequences</td>
</tr>
<tr>
<td><strong>Reported by</strong></td>
</tr>
<tr>
<td>patient</td>
</tr>
<tr>
<td>treating physician</td>
</tr>
</tbody>
</table>

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. 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. 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 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. 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. In some studies, over 50% of the reported adverse reactions were classified as "possible" and less than 10% as "certain". In contrast, Classen et al. 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 recur during chemotherapy, 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. 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. 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.

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. Many studies have shown that the percentage of preventable ADRs is high and ranges over 50%.

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.

References


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