

# Correlation Between the Tyrosine Kinase Inhibitor Sunitinib - Dose, Schedule of Administration and Adverse Events

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*Sunitinib, a multi-targeted receptor tyrosine kinase inhibitor, has demonstrated survival benefit in patients with metastatic renal cell carcinoma (mRCC) and is generally well tolerated with most adverse events, manifesting as mild to moderate in severity. The most frequent related adverse events include hand-foot syndrome (HFS), hypertension, proteinuria, cardiac toxicities, myelosuppression, fatigue/asthenia, hypothyroidism, diarrhea and hepatotoxicity. The study aims to determine incidence of adverse events among patients with metastatic renal cell carcinoma (mRCC) treated Sunitinib within five years from 2010 to 2015 and comparing the results with data from literature. The study included a total of 56 patients treated with Sunitinib, with a dose of 50 mg (Schedule 4/2). Due to adverse events and individual safety and tolerability, at the indication of the personal clinician, 11 patients needed dose reduction, with a continuous dose of 37.5 mg, daily and 28 patients continued the dose of 50 mg taken daily, on a different schedule (2/1 schedule). The most important toxicities were anemia, leukopenia, thrombocytopenia, gastrointestinal effects (diarrhea), fatigue and hypertension. After dose reduction or modified schedule the incidence of the most frequent toxicities (HFS, leukopenia, thrombocytopenia and fatigue) decreased, but hypertension was still observed in 30% of patients. The results are similar with data from literature. Early identification of individuals at risk and monitoring patients during Sunitinib treatment is very important and it can facilitate early intervention with prophylactic measures or supportive treatment, thus increasing quality of life and adherence to treatment. Further studies need to establish which targeted population can benefit the most from adjusted regimens and to correlate them with prognostic factors for survival.*

*Key words: Sunitinib, tyrosine kinase inhibitor, adverse events, schedule, dose reduction, tolerability*

Sunitinib is a small molecule multikinase inhibitor that impedes cellular signaling by targeting tyrosine kinase (RTK) receptors. These include platelet-derived growth factor receptors (PDGF-R) and vascular endothelial growth factor receptor (VEGF-R) receptors. So Sunitinib has an antiangiogenic and antitumoral effect. It also inhibits CD117 (c-KIT), the tyrosine kinase receptor involved in the pathogenesis of gastrointestinal stromal tumors. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(diethylamino) ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene) methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is  $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ . The capsules are supplied as printed hard shell capsules containing Sunitinib malate equivalent to 12.5 mg, 25.00 mg, 37.5 mg or 50.00 mg of Sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients [1-7].

Is used in the treatment of renal cancers, gastrointestinal stromal tumors (GIST) and well differentiated pancreatic neuroendocrine tumors (pNET). Recommended doses range between 37.5-50.00 mg per os per day. For the 50 milligrams oral dose once daily, administration is for 4 consecutive weeks, followed by a 2-week free period (Scheme 4/2), a complete cycle of 6 weeks. For gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (mRCC), the recommended dose of Sunitinib is 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period to comprise a

complete cycle of 6 weeks (Schedule 4/2). Administration can be done with or without food. Dose interruptions may be required based on individual safety and tolerability. Some studies analyzed, as part of therapy management, if the regimen may be changed to a 2-weeks on/1-week off regimen (schedule 2/1) based on individual safety and tolerability. For gastrointestinal stromal tumors and renal cancers, doses can be changed by 12.5 mg, depending on individual safety and tolerance. The daily dose should not exceed 75 mg and should not be less than 25 mg. For pNET, doses can be changed by 12.5 mg depending on individual safety and tolerance. The maximum dose administered in the Phase 3 pNET study was 50 mg per day. Dose discontinuation may be required [1, 2, 8-10].

Most common side effects are: myelosuppression, hypertension, hypothyroidism, skin erythema, skin dryness, yellowing of the skin, taste disturbances, hand foot syndrome (HFS), vomiting, diarrhea, lack of appetite, fatigue, asthenia. Less common side effects include epistaxis, heart dysfunction, liver failure, respiratory failure, intestinal perforation, pancreatitis. Hepatitis, hepatic failure, thromboembolic events, mandibular osteonecrosis, prolonged QT interval are among the rare side effects. Sunitinib could have possible drug interactions with inhibitors or inducers of the cytochrome P450 enzyme CYP3A4 (ketoconazole, rifampicin) and should be co-administered with caution. Temporary discontinuation of Sunitinib therapy is recommended for patients undergoing major surgical procedures [1, 2, 11-14].

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## Experimental part

### Objectives. The Main Objective

The primary study objective is to determine the incidence of adverse events among patients diagnosed with metastatic renal cell carcinoma (mRCC) and treated with tyrosinkinazine inhibitor Sunitinib and comparing the results with data from literature.

### Secondary Objectives

Establishing the proportion of patients who benefit from dose reduction or schedule modification regarding adverse events, following treatment with Sunitinib.

## Material and methods

### Study group

The study aims to determine incidence of adverse events among patients with metastatic renal cell carcinoma (mRCC) treated with tyrosinkinazine inhibitor Sunitinib at the Institute of Oncology Prof. Dr. Al. Trestioreanu within five years from 2010 to 2015. Between January 2010 and December 2015, a total of 78 patients were treated with Sunitinib, with a dose of 50 mg taken orally, once, daily, for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks (Schedule 4/2). The study group consisted of 56 patients diagnosed with metastatic renal cell carcinoma (mRCC), treated with Sunitinib in first or second line. The median age of treated patients was 58.5 years with variations ranging from 40 <years and> 77 years.

The experimental procedures were carried out in accordance with the mandatory principles of the ethics in clinical studies [15, 16].

### Inclusion and exclusion criteria

The *inclusion criteria* in this retrospective study contain the following: patients over 18 years old; metastatic renal cell carcinoma (mRCC) treated with Sunitinib in first or second line; clear cell histology; favorable/intermediate risk patients according to Memorial Sloan-Kettering Cancer Center (MSKCC) risk level for survival; Karnofsky performance status  $\geq 80\%$ .

*Exclusion criteria* included renal carcinoma with no clear cell component, patients whose clinical state and comorbidities are not consistent with administration of Sunitinib at the initial dose of 50 mg/day 4 weeks out of 6, Karnofsky performance status < 80%, poor risk patients according to Memorial Sloan-Kettering Cancer Center (MSKCC) risk level for survival, abnormal blood pressure at the time of initiation of Sunitinib in patients with previously diagnosed arterial hypertensive disease, major surgery within 4 weeks before Sunitinib initiation.

### Investigative Protocol

The experimental protocol includes the following steps:

- History and clinical examination (clinical examination on the body systems, including assessment of vital signs like temperature, pulse, blood pressure, respiratory rate, diuresis) before every cycle. All patients with previously diagnosed arterial hypertensive disease had to have normal blood pressure at the time of initiation of Sunitinib;

- Clinical examination of skin and mucous area before every cycle;

- Biological examination and adequate organ function before every cycle (absolute neutrophil (N) count  $\geq 2000/\mu\text{L}$ ; platelets  $\geq 150\,000/\mu\text{L}$ ; haemoglobin  $\geq 12\text{ g/dL}$ ; serum calcium  $> 8.8\text{ mg/dL}$ ; creatinine clearance  $\geq 30\text{ mL/min}$  - by the MDRD formula; total bilirubin  $\leq 1.5 \times \text{ULN}$  (upper

limit of the normal range); AST  $\leq 2.5 \times \text{ULN}$  and ALT  $\leq 2.5 \times \text{ULN}$  or AST and ALT  $\leq 5 \times \text{ULN}$  if liver abnormalities due to liver metastases (AST = aspartate aminotransferase; ALT = alanine aminotransferase);

- Normal thyroid function - thyroid-stimulating hormone (TSH) range 0.27-4.20  $\mu\text{UI/mL}$ , prior to administration of first dose of Sunitinib and every 3 months or when needed throughout treatment;

- Echocardiographic determination of left ventricular ejection fraction (LVEF) performed prior to administration of first dose of Sunitinib or when needed throughout treatment (normal LVEF was seen over 50%).

### Study type and statistical analysis

This study is an observational retrospective descriptive study type, which analyzed data from medical records in the archives of the Institute of Oncology Prof. Dr. Al. Trestioreanu within four years from 2010 to 2015. Data for the analysis were collected from the observation sheets and entered into the database. Retrieved data was analyzed with Microsoft Office Excel 2016.

## Results and discussions

The total number of patients who were included according to criteria set was 56 patients (72% of the total number of patients treated in the period determined), is presented in figure 1. Patients with metastatic renal cell carcinoma (mRCC) were treated with Sunitinib, with a dose of 50 mg taken orally, once, daily, for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks (Schedule 4/2). The study group consisted of 56 patients diagnosed with metastatic renal cell carcinoma (mRCC), treated with Sunitinib in first or second line. The study group comprised 34 men and 22 women.

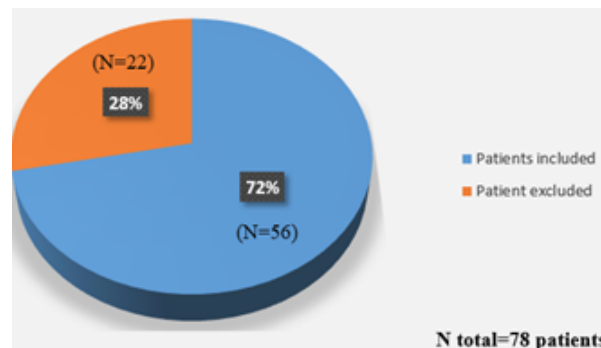


Fig. 1. Total number of patients included

Distribution through the years was as following: 2010 - 6 patients; 2011 - 9 patients; 2012 - 8 patients; 2013 - 11 patients; 2014 - 10 patients; 2015 - 12 patients. Total = 56 patients (fig. 2). From the total of 56 patients included, 75 % of them received Sunitinib in first line - 42 patients (fig. 3).

From the total number of 56 patients with metastatic renal cell carcinoma (mRCC) treated with Sunitinib, with a dose of 50 mg taken orally, once, daily, for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks (Schedule 4/2), 11 patients (20%) needed dose reduction due to adverse events, with a continuous dose of 37.5 mg, daily and 28 patients (50%) continued the dose of 50 mg taken daily, but in 2 consecutive weeks, followed by a 1-week rest period (2/1 schedule). This was necessary due to adverse events and individual safety and tolerability and was made at the indication of the personal clinician (tabel 1).

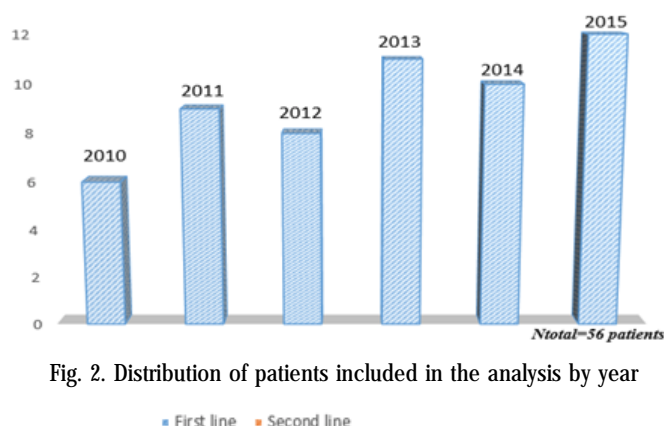


Fig. 2. Distribution of patients included in the analysis by year

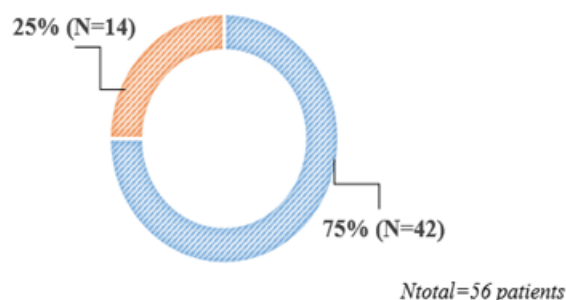


Fig. 3. Patients treated with sunitinib in first or second line

**Table 1**  
PATIENT DISTRIBUTION BASED ON DOSE AND SCHEDULE

Dose and schedule	Patients (N = 56)
50 mg (4/2)	17
50 mg (2/1)	28
37.5 mg	11

The most important toxicities were anemia, leukopenia, thrombocytopenia gastrointestinal effects (diarrhea, mucositis, stomatitis), fatigue and hypertension. Dose reductions were noted in 11 of the 56 patients. The following Grade 3/4 adverse reactions according to Common Terminology Criteria for Adverse Events (CTCAE) were observed: fatigue, diarrhea, anemia, hypertension and HFS. 28 patients continued the 50 mg dose, taken daily, but schedule was changed (2 consecutive weeks, followed by a 1-week rest period -2/1 schedule) because of the poor tolerability and to increase adherence to treatment. The

adverse events leading to schedule modification are summarized in table 2. Before dose or schedule modification 44% of patients presented HFS, 30% diarrhea, 35 patients fatigue and a third of patients (35%) hypertension. Hypothyroidism was seen in 30% of patients. After dose reduction or modified schedule, the incidence of HFS, leukopenia, thrombocytopenia and fatigue decreased, but hypertension was observed in 30% of patients, being one of the most common adverse event in this group of patients (table 2).

The toxicity profile of the 3 groups after switching to the modified schedule or dose is described in Table 3. Group A included patients on 50 mg daily dose of Sunitinib, for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks (Schedule 4/2). The most frequent adverse reactions were hypertension in 25% of patients, anemia (5 patients) and HFS. Group B included patients with Sunitinib continuous dose of 37.5 mg, daily and Group C patients on 2/1 schedule (50 mg of Sunitinib daily, but in 2 consecutive weeks, followed by a 1-week rest period). Two of the most common toxicities, leukopenia and HFS were less common in this subgroup, with 13% and respectively 11% of patients presenting them. Grade 3/4 adverse events (AE), according to CTCAE, was the same in the subgroups and the AE involved were similar. Three patients were diagnosed with grade 3/4 anemia (both in the 37.5 mg group and in the 50 mg schedule 2/1 group) and 1 patient in each group of the 50 mg dose (2/1 and 4/2 schedule) was diagnosed with grade 3/4 HFS. Hypertension and dysfunction of the thyroid were diagnosed in all groups, with similar incidence. Comparing the three arms regarding AE's, incidence of hypertension was lower only in Group B, leukopenia, thrombocytopenia, hepatotoxicity and HFS had a lower incidence both in the dose reduction group (B) and modified schedule group (C). No left ventricular dysfunction was diagnosed. Study limitations include: small cohort (normally require a larger sample size); direct access to patients (only medical records in the archives were analyzed), the decision of switching was made at the indication of the personal clinician; these findings may not translate to patients of other ethnicities.

Sunitinib, a multi-targeted receptor tyrosine kinase inhibitor, has demonstrated survival benefit in patients with metastatic renal cell carcinoma (mRCC) and is generally well tolerated with most adverse events, manifesting as mild to moderate in severity. The most frequent related adverse events include HFS, hypertension, proteinuria, cardiac toxicities, myelosuppression, fatigue/asthenia,

Adverse Events	Before Dose Modification N patients (%)	After Dose/Schedule Modification N patients (%)
Hand foot syndrome	25 (44%)	11 (20 %)
Hypertension	19 (35%)	17 (30 %)
Hypothyroidism	17 (30%)	13 (24%)
Leukopenia	15 (28%)	9 (16 %)
Thrombocytopenia	10 (18 %)	3 (5 %)
Anemia	30 (35 %)	22 (30%)
Diarrhea	16 (30%)	14 (25%)
Hepatic function laboratory abnormalities	5 (10%)	1 (1.78 %)
Fatigue	35 (60%)	14 (25 %)

**Table 2**  
ALL GRADES ADVERSE  
EVENTS BEFORE AND  
AFTER DOSE/SCHEDULE  
MODIFICATION



**Table 3**  
THE TOXICITY PROFILE OF THE PATIENTS AFTER SWITCHING TO THE MODIFIED SCHEDULE OR DOSE

ADVERSE EVENTS	GROUP A (4/2-50 mg) N = 17		GROUP B (37,5 mg) N = 11		GROUP (2/1-50 mg) N = 28		TOTAL
Grade	1/2	3/4	1/2	3/4	1/2	3/4	
<i>Cardiovascular</i>							
<b>Hypertension</b>	6 (25%)	0 (0%)	2(18%)	1 (9%)	8 (28%)		17
<b>LVEF dysfunction</b>	0	0	0	0	0	0	0
<i>Myelosuppression</i>							
<b>Leukopenia</b>	4 (25 %)	0	2(14%)		3 (13%)		9
<b>Anemia</b>	5 (28%)	2 (11%)	3 (25 %)	1 (9%)	8 (29 %)	3 (10%)	22
<b>Thrombocytopenia</b>	2 (11%)	0	0	1 (3%)	0	0	3
<b>Hepatotoxicity</b>	1 (5%)	0	0	0	0	0	1
<b>Hypothyroid</b>	4 (28%)	1 (5%)	3 (27%)	1 (9%)	4 (14%)	0	13
<b>Hand foot syndrome</b>	5(30%)	1(5%)	1 (9%)	0	3 (11%)	1 (4%)	11

hypothyroidism, diarrhea and hepatotoxicity. A good management of these adverse events with prophylactic measures, communication between patient and clinician can limit the dose reductions imposed and the patients can benefit with a better and longer response to treatment and a superior quality of life [1-3, 17].

The standard dosing schedule for metastatic renal cell carcinoma (mRCC) of Sunitinib is 50 mg daily for 4 weeks on, 2 weeks off (Schedule 4/2) or 37.5 mg taken orally once daily without a scheduled rest period. Dose interruptions may be required based on individual safety and tolerability. As part of therapy management, the treatment regimen may be changed to a 2 - weeks on/1-week off regimen (Schedule 2/1) based on individual safety and tolerability. Some prospective and several retrospective studies explored the Schedule 2/1 regimen aiming for improved safety without compromising efficacy of Sunitinib treatment. In a Phase 3 trial in first-line mRCC patients, Lee et al. analyzed the timing of onset of adverse events and their resolution. In conclusion, great part of adverse reactions occurred in weeks 3-4 and resolved during the rest period (weeks 5-6). The authors suggested that alternative dosing schedules such as Schedule 2/1 might improve the patient's tolerability to Sunitinib. The European Association of Urology (EAU) Guideline on RCC included Schedule 2/1 as an alternate scheduling option to manage toxicity [1, 2, 18-20].

Neri et al., [21] published in 2013 the results of a non-randomized Phase II study to evaluate whether Sunitinib 50 mg on schedule 2/1 could maintain the same dose-intensity as the standard 4/2 schedule, and provide the same efficacy, while reducing drug-related toxicity. 31 patients were enrolled in this study. Before the start of the study, 10 patients had received Sunitinib 50 mg daily on the schedule 4/2 that was modified to the schedule 2/1 when toxicity of Grade  $\geq 2$  was documented. At the same

time, 21 other patients were enrolled and received Sunitinib 50 mg/day on the schedule 2/1 from the beginning of the study. It concluded that Sunitinib 50 mg given orally on a schedule 2/1 can provide a high response rate, avoid drug-related toxicities and could achieve the same dose intensity as the standard schedule [21].

In our study 56 patients diagnosed with metastatic renal cell carcinoma (mRCC), treated with Sunitinib in first or second line received Sunitinib with a dose of 50 mg taken orally, once, daily, for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks (Schedule 4/2). From the study group, 11 patients needed dose reduction due to adverse events, with a continuous dose of 37.5 mg, daily and 28 patients continued the dose of 50 mg taken daily, but in 2 consecutive weeks, followed by a 1-week rest period (2/1 schedule). This was necessary due to adverse events and individual safety and tolerability was made at the indication of the clinician.

In our analyses the most important toxicities were anemia, leukopenia, thrombocytopenia gastrointestinal effects (diarrhea, mucositis, stomatitis), fatigue and hypertension. Grade 3/4 adverse reaction according to CTCAE was also noted: fatigue, diarrhea, anemia, hypertension and HFS. 44 % of patients presented HFS, 30% diarrhea, 35 patients fatigue and a third of patients (35%) hypertension. Hypothyroid was seen in 30% of patients. 11 patients (20%) continued the 50 mg dose, taken daily, but schedule was changed (2 consecutive weeks, followed by a 1-week rest period -2/1 schedule and dose reductions were noted in 28 (50%) of the 56 patients). After dose reduction or modified schedule, the incidence of the most frequent toxicities (HFS, leukopenia, thrombocytopenia and fatigue) decreased, but hypertension was observed in 30 % of patients, being one of the most common adverse event in this group of patients 17 patients (30%).

In 2014 Najjar et al., [22] conducted a retrospective review evaluating the tolerability of the treatment with Sunitinib on the modified schedule 2/1. The medical records of 30 mRCC patients were retrospectively reviewed. The schedule was changed after experiencing toxicity from a Schedule 4/2 to a Schedule 2/1 at the indication of the clinician. Ninety-seven percent of patients on the Schedule 4/2 had Grade 3/4 toxicity which led to the schedule change to 2/1. Half of the patients (53%) were dose reduced prior to switching to Schedule 2/1. Also, almost 50% of patients presented HFS, 40% diarrhea, 70% fatigue (21 patients) and 27% hypertension. After schedule change to 2/1, 17% of patients presented HFS, only 11 diarrhea; fatigue was observed in only 16% of patients and hypertension remained at the same incidence as the 4/2 schedule. The authors concluded that treatment with Sunitinib on a Schedule 2/1 was associated with significantly decreased toxicity in patients who initially experience Grade 3 or greater toxicity on the Schedule 4/2, two of the most common toxicities, fatigue and HFS, were significantly less frequent on the Schedule 2/1 than on the Schedule 4/2 and can extend treatment duration considerably and adherence to it [22]. In 2015 Bracarda and colleagues presented in *Annals of Oncology* the results of a multicenter retrospective study that evaluated the efficacy and safety of Sunitinib given on a Schedule 2/1 (460 patients with mRCC were enrolled). The results were similar as the study conducted, with a significant decrease of the incidence of toxicities [23]. Adjusted dose or modified schedule regimen can decrease toxicity, especially Grade  $\geq 3$  adverse events, increasing quality of life and treatment compliance, thus maybe improving progression free survival (PFS), possibly improving overall survival (OS) and reduce average monthly costs in Sunitinib-treated patients compared to the standard Schedule 4/2.

The most frequent related adverse events that we analyzed were HFS, hypertension, myelosuppression, fatigue, hypothyroidism, diarrhea and hepatotoxicity. No cardiac toxicities (left ventricular dysfunction) was observed. Grade 3/4 adverse reaction was observed: anemia, hypertension and HFS.

Before dose or schedule modification 35 patients presented fatigue (60%). After dose reduction, the incidence of fatigue decreased, only 25% of patients declaring persistent fatigue. The results of a retrospective study (45 Japanese mRCC patients who started on a Sunitinib schedule 4/2 but switched to a 2/1 schedule due to toxicity) showed that fatigue was more common in 4/2 schedule. The authors concluded that the 2/1 schedule showed a decrease in Sunitinib adverse events (especially relief from fatigue), improving quality of life and may therefore become the new standard dosing regimen [23].

Sunitinib is metabolized primarily by cytochrome P3A4 (CYP3A4), the CYP450 isoform, which produces its primary active metabolite, desethyl Sunitinib, which is then further metabolized by the same isoenzyme. Hepatotoxicity has been observed in patients treated with Sunitinib. Before every treatment cycle and as clinically indicated, adequate organ function should be verified (ALT, AST, bilirubin levels). If signs or symptoms of hepatic failure are present, Sunitinib should be discontinued and appropriate supportive care should be provided. Safety in patients with ALT or AST  $>2.5 \times$  ULN or, if due to liver metastases,  $>5.0 \times$  ULN has not been established. Sunitinib should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Co-administration of Sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of Sunitinib may be altered (like

ketoconazole, rifampicin). Lorenzo et al. indicated that hepatic toxicity is a class effect seen with vascular endothelial growth factor (VEGF) receptor inhibitors like Sunitinib. Approximately half of the patients exposed to these agents showed elevated transaminases. Antioxidant agents, such as N-acetylcysteine (600 mg/d) or glutathione (600–1200 mg/d) might be helpful in managing hepatotoxicity [1, 2, 24]. In the analyses presented here only one patient was identified with grade 1/2 hepatotoxicity (5%), in the 50 mg group, schedule 4/2.

In our study 44% of patients presented HFS before dose or schedule modification, and after dose reduction or modified schedule the incidence of HFS decreased, only 11 patients (20%) are being classified with adverse event. In group A (Sunitinib 50 mg- schedule 4/2) 5 patients (30%) presented grade 1/2 HFS and 1 patient (5%) grade 3/4. A lower incidence was observed in the other two groups. In group B (Sunitinib continuous dose of 37.5 mg) only 1 patient experienced HFS grade 1/2 and in the 50 mg Sunitinib 2/1 schedule group grade 1/2 was decreased by 19% and for grade 3/4 results were similar. Hand-foot syndrome (HFS), also known as palmar-plantar erythema presents as painful erythematous and edematous areas on the palms and soles, commonly accompanied by paresthesia, burning pain areas appearing after several days and can be aggravated in warm environments. It can be associated with skin dryness, rash, thickness or cracking of the skin. HFS may resolve and recur randomly, frequently among patients on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) and the symptoms generally worsen after 3 to 4 weeks of treatment, but they usually resolve during the off-treatment periods. Dose interruptions or dose modification in 12.5 mg steps may be required based on individual safety and tolerability. In a retrospective review of medical records at a Korean clinic from March 2007 to September 2008 assessing the skin toxicity of patients with solid tumors who were receiving Sorafenib or Sunitinib for at least 3 months, HFS was one of the most common skin events and was reported in 43 patients in the Sunitinib group (36%). 44% patients required temporary dose reductions. Puzanov et al., [25] conducted a retrospective analysis including pooled data from a total of 1186 patients from 9 prospective clinical trials (770 patients with mRCC and 416 patients with GIST) to investigate the correlation between Sunitinib-associated HFS and efficacy endpoints. The results showed that HFS was significantly associated with improved PFS and OS in patients with mRCC treated with Sunitinib and that HFS may be more reliable predictor of OS than PFS at early time points [1, 2, 25, 26].

Hypothyroidism has been reported as an adverse event of Sunitinib. Prospective and retrospective studies have reported the development of altered thyroid function in Sunitinib-treated patients. Overall, 7% of the mRCC population had either clinical or laboratory evidence of Sunitinib emergent hypothyroidism. Furthermore, several studies have shown a correlation between Sunitinib-induced thyroid dysfunction and clinical outcome of patients with metastatic renal cell carcinoma (mRCC). In this retrospective analysis, hypothyroidism was seen in 30% of patients with Sunitinib 50 mg schedule 4/2, with the same incidence after dose reduction or modified schedule. Baseline laboratory measurement of thyroid function is recommended in all patients. Routine monitoring of thyroid function should be performed every 3 months. As per medical practice standard thyroid replacement therapy with levothyroxine (LT4) should be initiated if hypothyroidism appears [1, 2, 27-29].

Sunitinib can determine modification in hematological parameters (leukopenia, thrombocytopenia or anemia). Hematologic toxicity may be a result of inhibition of receptors expressed on hematopoietic stem cells (KIT, PDGFR, FLT3). Adverse events are not cumulative and usually are reversible and do not result in treatment discontinuation, although Grade 3 and 4 cases have been reported. A complete blood counts should be performed at the beginning of each cycle. Many studies analyzed Sunitinib-induced toxicities such as leukopenia and thrombocytopenia, regarding incidence and possible use as efficacy biomarkers. In the Phase I study dose-escalation with Sunitinib administered by 4/2 schedule regimen hematologic safety parameters were analyzed. Both neutropenia and thrombocytopenia occurred. During the first 6 weeks of Sunitinib treatment, 1 of 9 patients (11%) on the recommended 50 mg/day dose experienced Grade 4 thrombocytopenia. Hematological toxicity resolved during the 2 weeks off period. Hong et al. evaluated hematologic toxicities in 136 mRCC patients treated with Sunitinib 50 mg 4/2 s schedule at a hospital in China. Hematologic parameters were measured at baseline and 14, 28, 42 (after a 2-week rest period) days with a median follow-up time of 23 months. The incidence of hematologic toxicity of Sunitinib varies in patient population in Asia versus US or Europe population. Retrospective analysis on 5 clinical trials involving 770 mRCC patients treated with Sunitinib, evaluated the use of treatment-induced toxicities such as myelosuppression as efficacy biomarkers. Patients received either a starting dose of Sunitinib 50 mg daily on Schedule 4/2 (N = 544) or Sunitinib 37.5 mg on a CDD schedule (N = 226). Neutropenia and thrombocytopenia were both statistically significantly associated with PFS and OS, thus indicating that neutropenia might be an independent prognostic factor. Sunitinib on 2/1 schedule is associated with decreased toxicity in metastatic renal cell carcinoma than 4/2 schedule [1, 2, 1, 30-33]. In the analyses presented in this paper, leukopenia and thrombocytopenia decreased after dose reduction or modified schedule, from 28% to 16% regarding leukopenia and 18% to 5% regarding thrombocytopenia. Both were more frequent in group A (Sunitinib 50 mg- schedule 4/2) than Sunitinib continuous dose of 37.5 mg group or the 50 mg Sunitinib 2/1 schedule group: 25% (4 patients) versus 14% (3 patients) versus 13% (2 patients) for leukopenia and 11% (group A) versus 3% (group B) for thrombocytopenia. No thrombocytopenia was observed in 50 mg Sunitinib 2/1 schedule group. Anemia was the most frequent adverse event regarding myelosuppression, with 5 patients (28%) in group A, 25% (3 patients in group B) and a higher incidence in group C- 29% of patients. All groups presented low grade and high-grade anemia, with 3 patients (10%) in 50 mg Sunitinib 2/1 schedule group and 2 patients in group A, respectively 1 patient in group B. Sunitinib can also induce temporary or reversible macrocytosis in mRCC patients and studies showed that it could potentially serve as a positive prognostic factor for survival [34, 35].

Probably one of the most frequent adverse events seen in patient treated with Sunitinib, arterial hypertension is 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. According to Rini et al., [36] this symptom is associated with a better response rate, and longer PFS and OS. Some patients were given antihypertensive drugs, and it is not entirely clear how this affects the data. Inhibition of VEGF by Sunitinib leads to vasoconstriction is possible result of reduced renal

excretion of sodium and water, reduced endothelial function and an elevated level of endothelin-1. Di Lorenzo et al. evaluated and explained in a retrospective analysis of 175 mRCC patients who received Sunitinib at 8 Italian institutions the risk for cardiovascular events. 59 (33.7%) patients included with preexisting hypertension. Seventeen (9.7%) patients developed grade 3 hypertension (3/17 of these patients were normotensive before Sunitinib); 14/17 of these patients developed hypertension after the third cycle of Sunitinib. There were 12 patients that experienced grade 3 LVEF (left ventricular ejection fraction) dysfunction, CHF (chronic heart failure) and grade 3 hypertension. Multivariate analysis suggested that the only significant independent predictors of CHF were a history of coronary arterial disease (CAD) (odds ratio (OR):18; 95% CI: 4-160;  $p = 0.005$ ) and hypertension (OR: 3; 95% CI: 1.5-80;  $p = 0.03$ ). Patients treated with Sunitinib, especially those with a previous history of hypertension and coronary heart disease, are at increased risk for CV events and should be monitored for exacerbations of their hypertension and for evidence of LVEF dysfunction during treatment. Aggressive management of blood pressure elevations is mandatory in preventing cardiac toxicity and increasing adherence to treatment [37-41].

In this observational retrospective descriptive study, hypertension was one of the most frequent identified AE before dose or schedule modification (35% of patients). All patients with previously diagnosed arterial hypertensive disease had to have normal blood pressure at the time of initiation of Sunitinib. The incidence after dose or schedule modification did not decrease significantly (17 patients-30%). In 7 patients with Sunitinib 50 mg - schedule 4/2, treatment continued because pharmacological equalization of the elevated blood pressure was achieved. For 5 patients, the Sunitinib dose was reduced to 25 mg/day (dose 37.5 mg daily) and for 3 patients the schedule was modified to Sunitinib 50 mg - schedule 2/1. Normalization of blood pressure was possible by using combinations of drugs with different mechanisms of action with the use of angiotensin-converting-enzyme (ACE) inhibitors (or sartans),  $\alpha$ -blockers, diuretics or calcium channel blocker, at the indication of the cardiologist. In one case, blood pressure returned to a normal level after stopping Sunitinib but continuation of antihypertensive drugs was necessary for the patient to receive again Sunitinib, this time with Sunitinib 50 mg- schedule 2/1. Hypertension was noticed with the same incidence in group A and C, confirming that hypertension due to Sunitinib is dose related with only 2 patients in group B, with a continues dose of Sunitinib of 35.5 mg presenting high values of arterial blood pressure after dose reduction. The blood pressure above was slightly above the normal range and could be influenced by numerous external factors. The retrospective study conducted by Miyake et al. on 45 Japanese mRCC patients who started on a Sunitinib Schedule 4/2 but were switched to a Schedule 2/1 due to dose limiting toxicity showed that hypertension was more common in 4/2 schedule than in 2/1 schedule, thus ameliorating toxicity and increasing efficacy, by improving quality of life and suggesting it as a new standard dosing regimen [23].

## Conclusions

Early recognition of adverse events can lead to improvement in progression free survival and patient outcomes. The focus of this review was to summarize Sunitinib most often side effects, highlighting the incidence of adverse events among patients with metastatic renal cell carcinoma (mRCC) treated with this tyrosinkinazine



inhibitor and the risk factors that can lead to these toxicities, thus improving strategies for surveillance and prevention. Some proportion of patients benefit from dose reduction or schedule modification regarding adverse events. The proportion of patients who experienced reversible adverse events in this study are similar to those presented in data from literature. Early identification of individuals at risk and monitoring patients during Sunitinib treatment is very important and it can facilitate early intervention with prophylactic measures or supportive treatment as per medical practice (cardioprotective medications like antihypertensive drugs, thyroid replacement, etc.) or dose/schedule adjustments to the regimen. A collaborative partnership between the oncologist and other specialists (cardiologist, dermatologist, endocrinologist) can facilitate the best care for cancer patients to limit further complications. Communication between patient and clinician can limit the dose reductions imposed and the patients can benefit with a better response to treatment and a superior quality of life. The standard dosing schedule for metastatic renal cell carcinoma (mRCC) of Sunitinib 50 mg (Schedule 4/2) can be changed to 37.5 mg daily without a scheduled rest period or the regimen may be changed Sunitinib 50 mg Schedule 2/1. As part of therapy management, the treatment should be based on individual safety and tolerability. Considering that there are no predictors of response to treatment, adverse reactions remain the only predictive factors associated with a good response to treatment, a better progression free survival (PFS) and overall survival (OS) to date. Schedule 2/1 may lead to longer treatment, resulting in a longer PFS. Further studies need to establish which targeted population can benefit the most from adjusted regimens and to correlate them with prognostic factors for survival.

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