SIDE EFFECTS OF SUNITINIB MANIFESTED ON SKIN OF PATIENTS DIAGNOSED WITH RENAL CELl CARCINOMA: CASE-CONTROL STUDY

Bojana Petrović1, Sinisa Radulović2 and Slobodan Janković1

Sunitinib is a small, lipophilic, synthetic molecule that interferes with tyrosine-kinase domain of vascular endothelial growth factor receptor, and prevents its activation after binding the vascular endothelial growth factor. Both in vitro and in vivo, sunitinib inhibits angiogenesis, and suppress growth of metastases, which depends on newly formed blood vessels. It was approved by FDA (U.S. Food and Drug Administration) in January 2006 for the treatment of advanced renal-cell cancer and imatinib-resistant gastrointestinal stromal tumours.

Among other adverse effects, it causes skin desquamation on fingers and toes, whitening of hair, eyebrows, mustache and beard.

The aim of our study was to prove the causal relationship between sunitinib administration and skin adverse effects.

The study involved the patients with metastasized renal cell carcinoma treated at the Institute for Radiology and Oncology of Serbia, in Belgrade. There were twelve patients (mean age 53.3 ± 11.1 years) who took sunitinib 50 mg daily, for 4 weeks ("cases"). Control group was composed of fourteen patients (mean age 54.6 ± 9.8 years) on standard therapy with interferon alpha (6 MJ three times weekly) and vinblastine 10mg, two days per cycle. The control patients were matched with "cases" by age, sex, phase of the disease and nephrectomy.

Out of the patients who received sunitinib, eleven (92%) patients developed desquamation on fingers and toes, whitening of hair, eyebrows, mustache and beard, while none of the skin adverse effects was observed in the control group (OR = 143). The distribution of hypertension, heart diseases and diabetes mellitus in the groups was not significantly different (p>0.05).

There is a strong association between administration of sunitinib in patients with renal cell carcinoma and observed skin adverse effects. Acta Medica Medianae 2009;48(4):5-8.

Key words: sunitinib, hand-foot syndrome, angiogenesis

Introduction

Sunitinib is a small lipophilic synthetic molecule, tyrosine kinase inhibitor which is the receptor for vascular endothelial growth factor. Sunitinib prevents activation of tyrosine kinase after its linking to vascular endothelial growth factor (1).

In "in vitro" and "in vivo" conditions, Sunitinib inhibits angiogenesis and prevents the expansion of metastasis, which depends on newly formed blood vessels. It was was approved by the FDA in January in 2006 for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) (1). It has been used in studies worldwide with relevant efficacy in patients with the aforementioned tumors.
Generally, sunitinib is very effective in these patients, but with side effects of usually medium or moderate severity (2). The most usual side effects in patients who use sunitinib are fatigue, diarrhoea, skin discoloration, and nausea (3). However, there are recent data about side effects on the skin, which are manifested by skin damaging and desquamation of hands and/or foot skin in patients who have been taking higher doses of the drug (≥75 mg a day) (4,5).

AIM

The aim of the study was to investigate a possible connection between palms and/or soles’ skin damaging and desquamation and the use of sunitinib in patients with metastatic renal cell carcinoma.

MATERIAL AND METHODS

The study involved the patients with metastatic renal cell carcinoma at the Institute for Oncology and Radiology of Serbia in Belgrade, from January 1, 2000 to April 1, 2007. There were 26 patients in total. The first group consisted of 12 patients who were taking sunitinib (50mg a day, for 28 days, followed by pause of 14 days, for 4 weeks) (“cases” in further text). The control group consisted of patients on standard therapy. In the “case” group there were 8 men and 3 women (average age 53.3 ±11.1). Whereas in the control group there were 11 men and 3 women (average age 54.6 ± 9.8).

All the patients were presented by age, gender, side effects on the skin, nephrectomy, chronic diseases (diabetes mellitus, hypertension, heart diseases) and the stage of carcinoma.

Statistics

In order to assess the risk of side effects manifestation on the skin in the group of patients who were taking sunitinib, we calculated the odds ratio (OR). The relevance of the differences between the “case” group and the control group was tested by Kolmogorov-Smirnov test or Student’s t-test for regularly distributed, continuous data (6). By means of multiple logistic regression (6), we tested a mutual influence of age and gender in patients who were taking sunitinib. All the calculations were obtained by SPSS statistic software, version 10.

Results

During the second out of three cycles of taking sunitinib, the side effects on the skin were noticed in 11 out of 12 patients. The manifestations appeared during the second cycle of therapy, followed by skin demaging and desquamation on palms and/or soles (Figure 2) and hair, eyebrows, beard and moustache depigmentation. After the termination of therapy, these changes diminished and withdrew.

Dermatological side effects were not noticed in the patients in the control group, neither during nor after the therapy. Odds Ratio for the side effects connected to sunitinib is 143.0.

The differences between groups of patients according to age, gender, nephrectomy, diabetes mellitus, hypertension, heart diseases and the stage of carcinoma did not show statistically significant differences between two groups (t = 0.34, p = 0.737; d = 0.11, p = 0.833; d = 0.07, p = 0.936; 0.07, p = 0.936; chi square = 0.004, p = 0.998; chi square = 0.13, p = 0.936 i d = 0.21, p = 0.552).

By using multiple logical regressions, we obtained the following values: p = 0.9256 with sunitinib therapy, 0.9572 for gender, 0.9484 for age >50 years old, unfavourable intersection of results (β). The value was very low to calculate the Odds ratio.

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Student’s t test

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Discussion

Although sunitinib is relatively devoid of hematological and gastrointestinal toxic effects, which are typical for classic antineoplastic forms, the skin damage on hands and feet was displayed even in 20% of patients. The syndrome also follows the classic neoplastic factors as fluorouracil and doxorubicin, but skin reaction on hands and feet caused by the use of sunitinib is clinically marked (7). Usual factors cause the display of extended redness and swellings followed by pain in palms and soles. In previous clinical studies, sunitinib was connected to the rash and skin desquamation, where skin became prone to bleeding (8,9).

In our patient, centralized skin deformations appeared, mostly on their feet, which was evenly followed by desquamation. Lesions did not cause much pain nor did they cause the discontinuity of therapy. Hair depigmentation was also centralized, of medium or moderate degree.

In available literature, no published reports on histological changes of skin lesions after the use of sunitinib were found. Nevertheless, from “in vitro” experiments and “in vivo” model we have seen that sunitinib prevents cells migration and weakens noticeably turbular formation of capillaries (10). Considering the frequency of skin side effects on palms and soles (>10%) (11), it seems that these manifestations are caused by action mechanisms of sunitinib, usually when it prevents metastasis of renal cell carcinoma by inhibiting capillary growth. It is probable that regeneration of palms and soles' capillaries is under high mechanical pressure during daily activities, blocked by sunitinib, causing epidermis proliferation and consequent desquamation.

Lesions on palms and soles require careful skin hygiene, and sometimes mild keratolytic agent. Patients should avoid long periods of standing and walking, for the purpose of decreasing abrasion of the irritated surfaces (9).

Conclusion

There is a strong association between administration of sunitinib in patients with renal cell carcinoma and observed skin adverse effects.

Contrary to the fact that the noticed side effects of sunitinib are of a moderate nature, further research of its pathophysiology is necessary as a precondition for development of useful strategies for prevention and reduction of their intensity.
NEŽELJENA DEJSTVA SUNITINIBA MANIFESTOVANA NA KOŽI KOD BOLESNIKA SA KARCINOMOM BUBREGA: STUDIJA SLUČAJ-KONTROLA

Bojana Petrović1, Siniša Radulović2 i Slobodan Janković1

Sunitinib je mali, lipofilni, sintetički molekul, inhibitor tirozin-kinaze, receptora za vaskularni faktor rasta. Sunitinib sprečava aktivaciju tirozin-kinaze nakon njenog vezivanja za vaskularni faktor rasta.

U „in vitro“ i „in vivo“ uslovima, sunitinib inhibiše angiogenezu i sprečava širenje metastaze, koja zavisi od novoformiranih krvnih sudova. Odobren je od strane FDA (Američka agencija za hranu i lekove) u januaru 2006. godine, za lečenje bolesnika sa metastatskim karcinomom bubrežnih elijia (RCC) ili bolesnika sa gastrointestinalnim stromalnim tumormapa (GIST) otpornih na imatinib.

Pored ostalih neželjenih dejstava, manifestovale su se promene na koži u vidu deskvamacije kože na prstima šaka i stopala, kao i depigmenzacije kose, obrva, brade i brkova.

Naša studija je dizajnirana sa ciljem da dokaže povezanost između primene sunitiniba i neželjenih dejstava manifestovanih na koži.

Studiija je sprovedena kod bolesnika sa metastatskim karcinomom bubrega lečenih na Institutu za onkologiju i radiologiju Srbije u Beogradu. Prvu grupu činili 12 bolesnika (prosečne starosti 53.3 ± 11.1 godina) koji su uzimali sunitinib 50 mg dnevno, 4 nedelje ("slučajevi"). Kontrolna grupa je sa 14 bolesnika (prosečne starosti 54.6 ± 9.8 godina) na standardnoj terapiji (interferon alfa (6 I.J. tri puta nedeljno) i vinblastin (10 mg dva dana u ciklusu)). Kontrolna grupa i grupa "slučajevi" bolesnika poređene su po starosti, polu, stadijumu karcinoma i nefrektomiji.

Kod bolesnika koji su uzimali sunitinib, kod njih 11 (92%) razvile su se deskvamacije kože na prstima šaka i stopala, kao i depigmentacija kose, obrva, brade i brkova.

Naša studija je dizajnirana sa ciljem da dokaže povezanost između primene sunitiniba i neželjenih dejstava manifestovanih na koži.

Ključne reči: sunitinib, deskvamacije kože, prsti, šaka, stopala, angiogeneza