Impact of Sunitinib Treatment on Blood Glucose Levels in Patients with Metastatic Renal Cell Carcinoma

Jong Jin Oh, Sung Kyu Hong*, Young Min Joo, Byung Ki Lee, Sun Ho Min, Sangchul Lee, Seok-Soo Byun and Sang Eun Lee

Department of Urology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

*For reprints and all correspondence: Sung Kyu Hong, Department of Urology, Seoul National University Bundang Hospital, 300, Gumi-dong, Bundang-gu, Seongnam, Kyunggi-do 463-707, Republic of Korea. E-mail: skhong@snubh.org

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Objective: To investigate the effects of sunitinib treatment on blood glucose levels in patients with metastatic renal cell carcinoma.

Methods: We reviewed the records of 48 patients who received sunitinib treatment for metastatic renal cell carcinoma between April 2007 and December 2010 at our institution. Patients’ data including diabetic status, diabetes mellitus medication and mean blood glucose levels before, during and after the treatment with sunitinib were assessed.

Results: In 10 of the 48 (20.8%) patients who were diabetic, the blood glucose level was observed to be significantly decreased after 4 weeks of sunitinib treatment with the mean decrease in blood glucose level being 76.1 ± 29.0 mg/dl (P = 0.002). Subsequently, after a 2-week off-treatment period, the mean blood glucose level rebound and increased (21.9 ± 6.3 mg/dl, P = 0.038) in these 10 patients. With sunitinib treatment, one patient was able to discontinue diabetes mellitus medication completely during a 4-week treatment period, and three other patients had dosages of their oral diabetes mellitus medication reduced. Among 38 non-diabetic patients, no significant changes in blood glucose levels were observed during both the 4-week sunitinib treatment period and the 2-week off-treatment period. No severe hypoglycemic episode was observed among our subjects.

Conclusions: Sunitinib treatment in diabetic patients with metastatic renal cell carcinoma may result in significantly decreased blood glucose levels. Thus, blood glucose levels should be checked more vigilantly in diabetic patients undergoing sunitinib treatment to adjust diabetes mellitus medications as needed. Further investigation via a larger scaled, prospective study would be needed.

Key words: renal cell carcinoma – sunitinib – glucose level – diabetes mellitus

INTRODUCTION

During the last decade, the treatment of metastatic renal cell carcinoma (mRCC) has evolved from being predominantly cytokine-based to being grounded in the use of new targeted agents (1). Certainly, an improved understanding of the molecular biology of mRCC has opened up a new era in the management of mRCC. Sunitinib is a tyrosine kinase inhibitor (TKI) currently approved for the use as a first-line therapy in the treatment of mRCC (2). It is known to inhibit tyrosine kinases, such as vascular endothelial growth factor, platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase-3, BRAF and c-KIT.

Although TKIs have offered improvements in oncologic outcomes compared with cytokine therapies, they are also associated with a certain degree of bothersome side effects. Common side effects of sunitinib include fatigue, diarrhea,
hand–foot syndrome, mucositis and hypertension (3). Meanwhile, besides well-known toxic effects of the two agents, we have observed in clinical practice that sunitinib had a certain effect on the blood glucose levels in some patients treated for mRCC. Looking at the literature, others have reported on similar observations (4,5). Some have even reported a case of remission of diabetes mellitus (DM) after sunitinib treatment (6). Thus, we investigated the effects of sunitinib treatment on the blood glucose levels in the patients with mRCC.

PATIENTS AND METHODS

With approval from institutional review board, we retrospectively analyzed the clinicopathologic data of 53 TKI-naïve patients who received sunitinib treatment for clear cell mRCC between April 2007 and December 2010 at our institution. For our study, we excluded the patients who had Eastern Cooperative Oncology Group (ECOG) performance status of ≥2, abnormal hematologic, coagulation, hepatic, renal and cardiac function at the start of TKI treatment. Also, those with no blood glucose level available or relevant data missing were excluded as well. Accordingly, a total of 48 patients were included in this study.

Patients’ data including age, gender, body mass index (BMI), extent of RCC metastasis, diabetic status, DM medication and mean blood glucose levels before/after the treatment with sunitinib were assessed. Before undergoing TKI treatment, all patients were routinely asked and checked via medical record review whether they had ever been diagnosed with DM. All DM patients included in our study had type-2 DM. In all patients, blood samples were taken at baseline and at the end of each treatment cycle.

The SPSS software package version 15.0 (Statistical Package for Social Sciences™, Chicago, IL, USA) was used for statistical analysis. Changes in blood glucose levels were analyzed by the non-parametric Wilcoxon test. Continuous variables were compared using the Mann–Whitney test, and categorical variables via the χ² or Fisher exact test. A two-tailed P < 0.05 was considered significant for all analyses.

RESULTS

Patient characteristics are shown in Table 1. The mean age of 48 total patients at the start of sunitinib treatment was 57.4 ± 11.5 years. Overall, 10 of the 48 (20.8%) patients were diabetics (all type 2) at the start of sunitinib treatments. Of the 10 DM patients, 9 were treated with oral DM medications and 1 patient was treated with insulin injection. The mean baseline blood glucose level at the start of sunitinib treatment was 123.6 ± 39.4 mg/dl among the 48 total patients. The mean number of cycles for sunitinib treatment given to our subjects was 6.9 ± 5.8.

For 10 patients who were diabetic, the mean baseline blood glucose level at the start of sunitinib treatment was 185.2 ± 52.8 mg/dl. In these 10 patients, the blood glucose level was observed to be significantly decreased after initial 4 weeks of sunitinib treatment with a mean decrease in the blood glucose level being 76.1 ± 29.0 mg/dl (P = 0.002) (Fig. 1). The change in blood glucose level was 41.1% after the initial cycle of sunitinib among diabetic patients. Subsequently, after the 2-week off-treatment period, the
mean blood glucose level rebound and increased (21.9 ± 6.3 mg/dl; \( P = 0.038 \)) and the percentage increase in the blood glucose level was 20.1%. During subsequent cycles of sunitinib treatment, blood glucose levels in DM patients showed similar trends of change (initial decrease and rebounding) as shown in Fig. 1. After three cycles of sunitinib treatment, one patient, who was taking glimepiride 4 mg per day, was able to discontinue the medication completely during the 2-week off-treatment period. In three other DM patients, dosages of oral DM medication were reduced with two to four cycles of sunitinib treatment. Meanwhile, no severe hypoglycemic event was observed among the 10 DM patients during their sunitinib treatments.

For 38 non-diabetic patients, the mean baseline blood glucose level at the start of sunitinib treatment was 107.8 ± 17.2 mg/dl. In these 38 patients, the mean blood glucose level of non-diabetic patients decreased (6.7 ± 0.9 mg/dl, \( P = 0.093 \)) after the first 4 weeks of sunitinib treatment and rebound to increase 2.5 ± 0.3 mg/dl (\( P = 0.604 \)) during the 2-week off-treatment period (Fig. 1). The change in blood glucose level was 6.2% decreased after the initial cycle of sunitinib among diabetic patients and 2.5% increased after off-treatment. No significant changes in blood glucose levels were observed during sunitinib treatment in these 38 patients. However, blood glucose levels of 76 non-diabetic patients also showed slight trends of decreasing with sunitinib treatment and increasing during the subsequent off-treatment period.

Data with regard to patients’ BMI at the start and at the end of sunitinib treatment were available in 9 of the 10 DM patients and 35 of the 38 non-diabetic patients. Among the nine DM patients, the mean BMI decreased (0.68 ± 0.12 kg/m\(^2\)) with sunitinib treatment (\( P = 0.298 \)). The mean decrease in BMI in 35 non-diabetic patients was 0.25 ± 0.22 kg/m\(^2\) (\( P = 0.345 \)). Thus, no significant changes in BMI were observed with sunitinib treatment among our subjects. Treatment-related oral disorders with sunitinib, which may include stomatitis, mucositis, mucosal hypersensitivity, oral ulcers and taste alteration, were observed in 20 (52.6%) of the non-diabetic patients and 6 (60%) of the diabetic patients. There was no significant difference between them (\( P = 0.446 \)).

**DISCUSSION**

In the current study, we observed that sunitinib treatment in patients with mRCC who also had DM resulted in significantly decreased blood glucose levels. In some DM patients, their medications for DM were discontinued or reduced with sunitinib treatment. On the other hand, sunitinib treatment was observed to have no significant impact on the blood glucose levels among the non-diabetic patients in our study.

Looking at the current literature, not many have specifically reported on the effects of TKI treatment on blood glucose levels. Templeton et al. (6) reported on a single case of a patient with both mRCC and type-1 DM who demonstrated a sustained normoglycemia without insulin treatment after 9 months of treatment with sunitinib. Also, Billemont et al. (4) reported from analyzing 19 mRCC patients with type-2 DM who underwent sunitinib treatment that all 19 patients had significantly decreased blood glucose levels after 4-week treatment. Such phenomenon was followed by an increase in blood glucose level during the 2-week rest period. Among the 19 patients, 2 patients were able to stop their DM medication during the treatment phase and reinitiated medication during the 2-week rest period. They found no severe episode of hypoglycemia in their patients. They also observed statistically non-significant decreases in blood glucose levels among nine non-diabetic mRCC patients as well. Changing trend of blood glucose levels over time appeared to be different for these nine non-diabetic patients with no variation during sunitinib therapy or in the 2-week off-treatment period. Such findings reported by Billemont et al. (4) can be considered quite similar to our results. Meanwhile, Agostino et al. (5) retrospectively studied the blood glucose levels in 17 patients with type-2 DM and 61 non-diabetics who were treated with dasatinib, imatinib, sunitinib or sorafenib for various malignancies. They also observed significant declines in blood glucose levels with all four types of TKI treatments. Notably, 47% of their subjects with DM were able to discontinue their DM medications with one DM patient developing symptomatic hypoglycemia while on sunitinib. In contrast to our findings, Agostino et al. (5) suggested that the magnitude of the effect of TKIs on blood glucose levels was similar in diabetic and non-diabetic subjects. Such difference in the observed findings may be due to a different analytic method of assessing blood glucose levels. Still, further investigation via a large-scale, prospective study would be needed to appropriately address the potential difference in the impact of sunitinib treatment between diabetic and non-diabetic patients.

Currently, the exact underlying mechanism for decline of blood glucose levels with TKI treatment remains elusive. It can be hypothesized that a decrease in oral intake with sunitinib treatment may have contributed. However, as no significant change in BMI was observed in our subjects, such possibility appears to be less likely. Some have suggested that TKI’s effect on c-KIT tyrosine kinase may be involved in the alteration of blood glucose levels since c-KIT has been reported to be associated with pancreatic \( \beta \)-cell survival from *in vitro* and animal study (7,8). Others have mentioned that quantitative and qualitative capillary regression in pancreatic islets due to TKI treatment may have played a role (9). In both the animal model and human, imatinib treatment has been observed to ameliorate DM (10,11). Such phenomenon was thought to be due to the protective effect of imatinib on \( \beta \)-cells by antiapoptotic action through nuclear factor-\( \kappa \)-B. Meanwhile, no such effect has been reported with regard to sunitinib. Rather than a direct effect on pancreatic cell mass, Billemont et al. (4) have raised the possibility of sunitinib having an impact on insulin resistance.
by interfering with IGF-1 pathway. Similarly, Hagerkvist et al. (12) observed that imatinib decreased insulin resistance and hepatic glucose production in a rat model. Although pathogeneses are different, type-1 and -2 DM may have overlapping inflammatory pathways. In mouse models, Louvet et al. (13) demonstrated that the inhibition of PDGFR would be critical to the reversal of DM by sunitinib and imatinib treatment. They suggested that inhibition of PDGF downstream-mediated inflammatory response may consequently hinder pancreatic β-cell death and insulin resistance. However, the possibility of other tyrosine kinases being responsible for alteration of glycemic control still exists. Further research on the exact mechanism of the glucose-lowering effect of TKI treatment may well lead to a novel therapeutic target for the treatment of DM. Meanwhile, the impact of sunitinib treatment on the blood glucose level was observed to more profound among DM patients compared with non-diabetics in our study as well as in others. One of the potential explanations for such phenomenon can be an interaction between sunitinib and DM medication. Further investigations are warranted on the issue.

Looking at the relevant reports as well as our data, it would be important for physicians to closely monitor the glycemic control in patients treated with TKI. Especially, DM patients who are taking hypoglycemic medications should be followed more closely to prevent a TKI-induced hypoglycemic event. Adjustment of dosage for DM medication at the start of TKI treatment could also be considered in such patients.

Our study is limited by its retrospective nature. Also, as aforementioned, fasting determination of blood glucose levels was not performed in all cases. Still, it should be noted that each patient tended to make visits to our clinic at the same hours, which would translate into patients providing blood samples at similar time during each visit. It should be reminded that dosage and type of patients’ DM medications could not be controlled for. Moreover, disease severity, regarding both DM and mRCC, could not be controlled for. Although no significant change in BMI was observed among our patients, possibilities of decreased intake or intestinal toxicity affecting the blood glucose level could not be completely ruled out from the current analysis.

CONCLUSIONS

Our results showed that sunitinib treatment in diabetic patients with mRCC may result in significantly decreased blood glucose levels, whereas no such observation was made in non-diabetic patients undergoing sunitinib treatment. Since a decrease in blood glucose levels may be more prominent among diabetic patients, blood glucose levels should be checked more vigilantly in diabetic patients to adjust DM medications as needed. Further investigation via a larger scaled, prospective study would be needed.

Conflict of interest statement

None declared.

References