

Effect of Tyrosine Kinase Inhibitors on Renal Functions



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Abstract

Background: We aim to document if any difference exists for renal functions between metastatic and non-metastatic patients.

Methods: The study population included 12 metastatic and 15 non-metastatic patients. Metastatic renal cancer patients using the TKIs were compared to non- metastatic patients.

Results: Preoperative estimated glomerular filtration rate (e-GFR) was significantly low in metastatic patients than non-metastatic patients (p: 0.048). A trend toward increased acute kidney injury during hospital stay in the non-metastatic group was observed, but this fell just short of statistical significance (p: 0.109). Two groups did not differ significantly in terms of postoperative e-GFR (p: 0.256). No statistically significant differences were observed in actual e- GFR between two groups (p: 0.638). No statistically significant differences were found in pre-TKIs and post-TKIs e-GFR values (p: 0.735). Proteinuria was statistically more common in metastatic patients than non-metastatic patients (p<0.001). No statistically significant difference in age, sex, follow-up period, NSAIDs use, antihypertensive and ARBs/ACEIs use were documented between the two groups.

Conclusion: Increased risk for proteinuria was documented in metastatic patients with TKIs use. However, use of the TKIs had no effect on e- GFR. No statistically significant differences were observed in actual e- GFR between two groups.

Keywords: Hypertension; Glomerular Filtration Rate; Proteinuria; Tyrosine- Kinase Inhibitors

Abbreviations: RCC: Renal cell carcinoma ; TKIs: Tyrosine-Kinase Inhibitors; AKI: Acute Kidney Injury; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ARBs: Angiotensin Receptor Blockers; ACEIs: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers; CCBs: Calcium Channel Blockers; e- GFR: Estimated Glomerular Filtration Rate

Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies [1]. Treatment options for the RCC include surgery, radiotherapy and immunotherapy [2]. Besides these options, molecular-targeted therapies in the form of tyrosine-kinase inhibitors (TKIs) are commonly used. These agents are well tolerated compared to previously used options (interleukin 2 or interferon- α) and the use of these agents results in longer progression-free survival and increased response rates [3-5]. Despite the advances achieved with these agents, use of the

TKIs results in side effects such as fatigue, nausea, diarrhea, gastrointestinal hemorrhage, dysphonia, and palmar-plantar erythrodysesthesia [6]. Hypertension and proteinuria are also usually encountered after the start of these agents [7-9]. In this study, we compared clinical features between patients with renal cell carcinoma with and without the TKIs treatment and aim to document if any difference exists for renal functions between metastatic and non-metastatic patients during their follow up period.

Material and Methods

The patients diagnosed with the RCC and followed up at Istanbul Health Sciences University Haydarpaşa Numune Education and Research Hospital oncology polyclinics between 2009 and 2016 were evaluated. Eligible 12 metastatic patients who received a nephrectomy and were treated with the TKIs were included in the metastatic group. Fifteen non-metastatic RCC patients who only received a nephrectomy formed the non-metastatic group. Metastatic patients who did not receive a nephrectomy, patients on dialysis, and patients with insufficient data were excluded. Patients' demographics and laboratory data were collected from the hospital records and via telephone. The clinical, demographic, and laboratory parameters were compared between the two groups. The data collected included patient age, sex, follow-up time, nephrology follow-up, mortality, history of perioperative acute kidney injury(AKI), use of non-steroidal anti-inflammatory drugs (NSAIDs), use of antihypertensive medications including angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), calcium channel blockers(CCBs), and alpha and beta blockers. The data also included laboratory parameters such as estimated glomerular filtration rate (e-GFR) (calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 2) and proteinuria (assessed using dipstick and 24-hour urine collection). Creatinine levels before the operations were used to calculate postoperative e-GFR, and postoperative creatinine levels taken just before hospital discharge were used to calculate postoperative e-GFR. Actual e-GFR was calculated using creatinine levels measured at the last hospital visit. Perioperative AKI was defined using the acute kidney injury network classification system. Increase in serum creatinine of 0.3 mg/dl or more within 48 hours or ≥ 1.5 times baseline within 7 days was used in order to define perioperative AKI. Urine volume was not used as a criterion because data for urine volume were not available.

The TKIs used as targeted therapy for our patients were sunitinib, pazopanib, and axitinib. Available creatinine measurements before and after the TKIs treatment were used to present the effect of the TKIs on renal function. Statistical analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013). The normality of continuous variables was investigated using the Shapiro-Wilk test. Descriptive statistics are

presented using the mean and standard deviation for normally distributed variables and median (and minimum–maximum) for the non-normally distributed variables. Student's t-test was used to compare two normally distributed groups. Non-parametric statistical methods were used for values with skewed distributions. The Mann-Whitney U test was used to compare two non-normally distributed groups. The χ^2 test was used for categorical variables and expressed as observation counts (and percentages). Statistical significance was accepted when the two-sided p value was lower than 0.05.

Results

The study population consisted of 22 males and 5 female patients. The mean age of study population was 59.2 ± 11.3 years. Clinical and laboratory parameters of metastatic and non-metastatic patients are listed in Table 1. Preoperative e-GFR was significantly lower in metastatic patients when compared to non-metastatic patients (p: 0.048). When two groups were compared, a trend toward the increased AKI during hospital stay in the non-metastatic group was observed, but this fell just short of statistical significance (p: 0.109). There was no statistically significant result between two groups when two groups were compared for postoperative e-GFR (p: 0.256). The statistically nonsignificant result for postoperative e-GFR between two groups was also observed for actual e-GFR (p: 0.638) and no statistically significant differences were found between pre-TKI and post-TKI e-GFR values (p: 0.735). Proteinuria was more common in metastatic patients than non-metastatic patients (p<0.001). In metastatic group 8 patients had proteinuria. Four patients out of these 8 patients had 24-hour proteinuria measurements. One patient had nephrotic range proteinuria and the other three patients had non-nephrotic range proteinuria. No biopsies were performed on these patients with proteinuria. Two metastatic patients had negative results for proteinuria. Data for dipstick proteinuria were unavailable for the other two patients. Only one patient in the non-metastatic group had proteinuria and it was at a level of less than 1 gr/day. There was no statistically significant differences in age, sex, follow-up period, NSAIDs use, antihypertensive and ARBs/ACEIs use, and follow-up time between metastatic and non- metastatic patients. Follow-up times for metastatic and non-metastatic patients were 29.9 ± 19.6 and 25.2 ± 9.4 months; respectively. Three patients died during the follow-up period and all were in the metastatic group.

Table 1: Clinical and laboratory parameters.

Parameters	Metastatic n:12	Non-metastatic n:15	p
Age(years); mean+SD;	61.4±13.9	57.4+8.8	0.371
Gender (male); n (%)	11 (91.7)	11 (73.3)	0.342
Follow-up time(months); mean+SD;	29.9 ± 19. 6	25.2±9. 4	0.467
Mortality; n (%)	5 (41. 7)	0	0.01
Diabetes Mellitus, n (%)	1 (8.3)	4 (30.8)	0.322
Hypertension; n (%)	5 (41.7)	5 (38.5)	1.00

Preoperative e-GFR(ml/min); mean+SD	60.9±25	85.4±16.2	0.048
Postoperative e-GFR(ml/min); mean+SD	51.6+22.3	67.0+22.8	0.256
Perioperative Acute Kidney Injury; n (%)	2 (33.3)	9 (81.8)	0.109
Actual e-GFR (ml/min); mean+SD	54.4±25.4	58.8±21.6	0.638
NSAIDs usage; n (%)	6 (50)	9 (60)	0.707
Antihypertensive usage*; n (%)	5 (41.7)	5 (38.5)	0.194
ARBs/ACEIs usage; n (%)	4 (33.3)	4 (26.7)	1.00
Nephrology visit; n (%)	6 (50)	8 (53.3)	1.00
Proteinuria with strip; n (%)	8 (80)	1 (7.1)	<0.001

e-GFR: Estimated glomerular filtration rate; NSAIDs: Non-steroidal anti-inflammatory drugs; ARBs/ACEIs: angiotension receptor blockers/ angiotension converting enzyme inhibitors; * antihypertensive use rather than ARBs/ACEIs

Discussion

Nearly all patients taking the TKIs experience a rise in blood pressure. Systemic vasoconstriction and volume overload are parts of the mechanisms responsible for systemic hypertension caused by TKIs [7]. Despite the risk of hypertension occurrence, the development of hypertension is mostly a good prognostic sign because it is associated with longer progression free and overall survival and can be used as a biomarker for tumor responsiveness [10]. Regarding our study, there was no statistically significant results between groups for ACEIs/ARBs and other antihypertensive use. Proteinuria is another important side effect that can be encountered after the start of targeted agents. In the kidney, the vascular endothelial growth factor pathway is known to be responsible for proteinuria after the start of TKIs [11]. In the study of Baek et al. [12] initiation of sunitinib therapy was related to proteinuria and aggravation of preexisting proteinuria in 17.6% and 23.1% of patients; respectively [12]. Again in the COMPARZ study, discontinuation of treatment because of proteinuria was observed in 3% and 1% the of patients treated with pazopanib and sunitinib; respectively [13]. In our study, most of the patients treated with the TKIs had proteinuria. However, only one patient had nephrotic-range proteinuria. We did not perform a renal biopsy on this patient but important data can be obtained through this procedure. Biopsy-proven acute interstitial nephritis, thrombotic microangiopathy and acute tubular necrosis have also been encountered after the TKIs use [14-16]. In our study, there was no statistically significant difference between pre-TKIs and pre-TKIs e-GFR values. However, patients can develop renal insufficiency during treatment with targeted agents. A study by Zhu et al. [17] showed the development of renal insufficiency in the RCC patients receiving sunitinib [17]. In our study, despite the statistically significant result for preoperative e- GFR in favor of non- metastatic patients, there was no statistically significant results for postoperative e-GFR between two groups which may be due to the high percentage of patients with AKI in the non-metastatic group. Despite the tumor burden and use of the TKIs in metastatic patients, the non-significant result for postoperative e-GFR between two groups did not change at last hospital visit. The small sample size and retrospective nature of the study are important limitations that should be considered. However, renal side effects encountered after use of the TKIs

were emphasized in this study with comparing metastatic and non-metastatic RCC patients. In conclusion, increased risk for proteinuria was documented in metastatic patients with TKIs use. However, use of the TKIs had no effect on e- GFR. There was also no statistically significant difference for the actual e-GFR between the two groups despite the higher preoperative e-GFR observed for non- metastatic patients.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional approval has been obtained.

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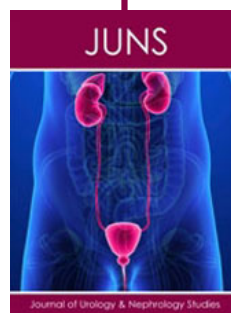
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