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Article / Makale

Alteration of thyroid functions in patients with renal cell carcinoma treated with tyrosine kinase inhibitors; Turkish population study.

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Abstract

Background Studies investigated different side effects of TKIs such as hypertension, dermatologic side effects and hormonal changes. Thyroid hormones change is take an interest for last decade and phase 2 and 3 trial result had been analyzed retrospectively for this reason.

Method A totally 246 metastatic renal cell carcinoma patients who were treated with TKI included in the study and they recruited from over 10 different oncology clinics.

Results In the study 246 mRCC patients included and mean age was 60 (±8), and 183 (74%) of them were male, 63 (24%) of them were female. Following TKI therapy 15 patients (6%) became as a hyperthyroidic, 83 patients (34%) became hypothyroidic and remaining 148 patients had in normal range for TSH levels. When we subgroup the patients according to the TSH change, in 38 patients (15.4%) had THS decreasing at least 50% from baseline and 128 patients (52%) has elevated THS levels as described previous range. In survival analyses, became hyperthyroidic patients had significantly longer OS than became hypothyrodic patients (25.4 vs 14 months, P=0.036) but no significantly differ than remained normothyroidic patients (25.4 vs 18 months, P=0.16).

Conclusion patients who had decreasing TSH levels under the treatment of TKI should have significantly higher overall survival but, hypothyroid patients don't.

Keywords THS, tyrosine kinase inhibitor, survival, predictive, renal cell carcinoma

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Introduction

The incidence of renal cell carcinoma (RCC) increasing in all world accounting for 2–3% of all cancers, and it was diagnosed with a median age at diagnosis of 65 years, and second common urologic cancer in the Turkey [1,2]. Renal cell carcinoma has an 85% of survival rate for 5-year, but about 30% of patients had been diagnosed with metastatic stage [3]. Present, there was no adjuvant targeted therapy for RCC, but metastatic RCC have many options such as sunitinib, sorafenib, pazopanb, everolimus, axitinib, temsirolimus, and bevacizumabq[4]. In lieu cytokines, targeted agents have longer progression-free survival (PFS) of around 7-9 months and overall survival (OS) about 2 years [5,6]. Tyrosine kinase inhibitors (TKI) sunitinib and pazobanib are the first line and everolimus and axtinib are the second line most common choice and covered the community health insurance in Turkey. TKIs are acting as block the ATP-binding site in tyrosine kinases and change the cell proliferation, metastasis, or angiogenesis by inhibiting signal transduction. Despite their mechanism of action is similar, they have different pharmacokinetics and side effects[7]. Many studies investigated different side effects of TKIs such as hypertension, dermatologic side effects and hormonal changes. Thyroid hormones change is take an interest for last decade and phase 2 and 3 trial result had been analyzed retrospectively for this reason. In this study we investigated thyroid stimulant hormone change with TKI therapy and relation between the oncologic outcomes in Turkish patient population.

Materials and methods

Patients

A totally 246 metastatic renal cell carcinoma patients included in the study and they recruited from over 10 different oncology clinics. All patients were pathologically confirmed with renal cell carcinoma. All patients treated with TKIs, suntinib, sorafenib, pazopanib or axitnib or everolimus as mTOR inhibitor due to their stage and line of therapy. According to the our community health system we usually start with either pazopanib or sunitinib as a first choice of mRCC treatment. The following characteristics obtained from patients' charts: age, gender, body mass index, histopathology, diagnosis time, type of TKI, date of progression time, date of last visit, responses to treatment and survival.

Laboratory parameters obtained from the hospital records: thyroid stimulant hormone level measured at baseline and following the 8-12 weeks of treatment as a control. Response evaluation made by according to response evaluation criteria in solid tumors-1.1 (RECIST-1.1) criteria every three months.

Inclusion criteria were diagnosis metastatic renal cell carcinoma. Exclusion criteria were any thyroid disease and using medication for this, withhold the TKI therapy less than 4 weeks,

Study Design

Patients had categorized into "TSH decrease" or "TSH increase" groups accepted at least 50% of change from the base line, and becoming "hyperthyroidic", "hypothyroidic" or "stay in normal range". The study protocol approved by the institutional review board and written informed consent obtained from all participants. Progression-free survival (PFS) was defined as the time between the diagnosis and disease progression, whichever occurred first. Overall survival (OS) was calculated as the time between the diagnosis and death or last follow-up.

Statistical analyses

All statistical tests were performed by using software (SPSS 21 inc USA). The distribution of variables normality tested with Kolmogorov–Smirnov test and presented as mean ± standard deviation (SD) median and interquartile ranges, as appropriate. Differences between survivor and died patient's variables according to distribution evaluated by the unpaired t test, and Mann–Whitney U test, respectively, as appropriate. The Wilcoxon signed-rank test used to compare the change in serum TSH levels between baseline and after first and 3rd month of TKI therapy. For each covariate, the univariate and multivariable associations with OS and PFS were conducted using the Cox proportional hazards model. A P value <0.05 was considered as statistically significant.

Results

In the study 246 mRCC patients included and mean age was 60 (±8), and 183 (74%) of them were male, 63 (24%) of them were female. Median follow up period was 24 months. The median OS was 15.4 months, and median PFS was 8 months. The mean serum basal TSH level was 2.3 mIU/L and after the

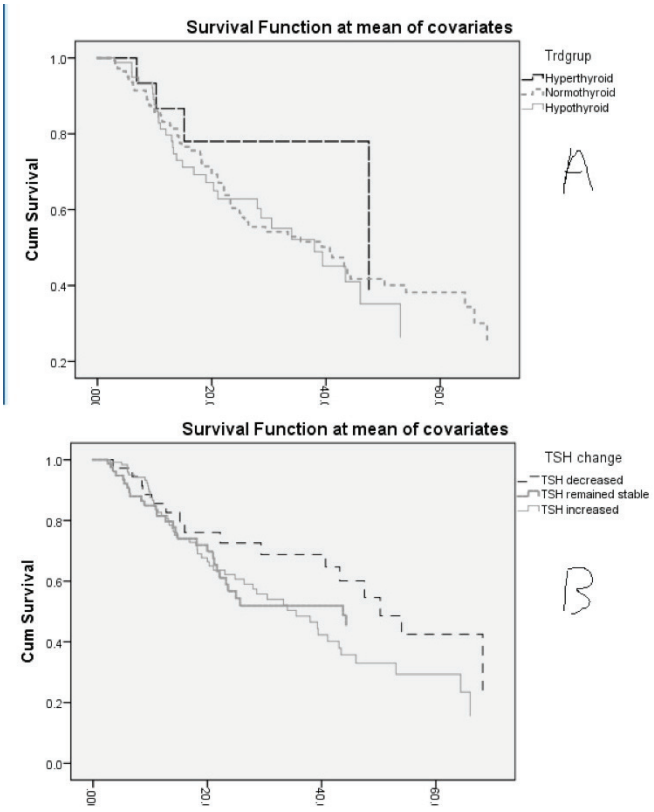
TKI therapy control mean TSH level was 10.2 mIU/L. The most common used tyrosine kinase (TKI) were, 163 (66%) of sunitinib, 47 (19%) of pazopanib, and 15 (6%) of sorefenib. As a second or third line, 21 patients received axitinib or everolimus.

Following TKI therapy 15 patients (6%) became as a hyperthyroidic, 83 patients (34%) became hypothyroidic and remaining 148 patients had in normal range for TSH levels. When we subgroup the patients according to the TSH change, in 38 patients (15.4%) had THS decreasing at least 50% from baseline and 128 patients (52%) has elevated THS levels as described previous range. We summarized this finding in table 1.

Table 1. Survival outcomes and TSH levels in patient's subgroup

Characteristic	Hypothyroidic N=83	Normothyroidic N=148	Hyperthyroidic N=15
Overall survival, months	14	18	25.4
Progression free survival, months	8	8	9.8
TSH baseline, mIU/L	2.2	2.2	3.5
TSH after therapy, mIU/L	8.5	2.5	0.21
	TSH increased N=128	TSH stayed stable N=80	TSH decreased N=38
Overall survival, months	15	14.5	27.4
Progression free survival, months	8	8	11.5
TSH baseline, mIU/L	1.8	2	4.6
TSH after therapy, mIU/L	9.4	1.8	1.3

In survival analyses, became hyperthyroidic patients had significantly longer OS than became hypothyrodic patients (25.4 vs 14 months, P=0.036) but no significantly differ than remained normothyroidic patients (25.4 vs 18 months, P=0.16). When we analyzed according to the TSH change, TSH decreased group had significantly longer OS compared to the both other groups (27.4 vs 15 months, P= 0.033, 27.4 vs 14.5 months, P=0.017). For progression, free survival analyses, there were no any significant relations between the groups. Figure 1A and B showed the OS analyses of the comparisons.



Discussion

This is the first study reporting TKI toxicities about thyroid dysfunctions in Turkish population. Consistent with the literature TKI therapy cause quite common thyroid stimulant hormone changes. In our population TKI therapy caused 34% of hypothyroidism and 6% of hyperthyroidism during the first 3 months of therapy. Also, we investigated the changing of TSH levels, not only transforming as a hypertyroidic or hypothyroidic, more patients had THS altering, 50% of patients THS was elevated and 15% of population had decreased THS levels. Additionally, decreasing THS levels was significantly associated with longer overall survival but not progression free survival. Elevating TSH had no significantly impact on oncologic outcomes.

Targeted therapies either TKI, angionesis inhibitor or mTOR inhibitor had many common side effect profiles such as fatigue, diarrhea, nausea, anorexia, rash, hand–foot skin reaction, cardiovascular side effects such as heart failure and hypertension [4]. In last decade, many thyroid dysfunctions had been reported during TKI therapies. Target agents affect the thyroid homeostasis, but exact mechanisms are not well known. Severe hypothyroidism had been reported with these agents in mRCC but, typically can be easily treated with thyroid hormone replacement therapy [8].

Sunitinib is one of the most common TKI used for mRCC, Motzer et al. presented in a phase 3 trial, they found 24% of hypothyroidism and 2% of them grade 3-4 [9]. Retrospective and prospective studies have indicated that sunitinib can cause hypothyroidism in a 50-85% [4,10,11]. Sorafenib-induced hypothyroidism does not common as sunitinib-induced hypothyroidism, studies showed aroun 10-20% of hypothyroidism [11,12] as well as pazopanib was found around 10% [9,13]. The mechanism is not well defined by new studies support that VEGF inhibition is one of the component of the etiology[4]. The influence of hypothyroidism on oncologic outcomes has been investigated in several studies. A report on patients treated with sunitinib found that hypothyroid patients had significantly longer PFS than euthyroid patients [14]. Another study compared sunitinb with sorafenib, found 44% vs 27% hypothyroidism respectively, and there was a significantly higher PFS rates compared to euthyroid (18 vs 10 months)[15]. Sella et al. found longer PFS and OS in patients who become hypothyroid[16]. Despite to these data, a prospective study showed that 53% of 102 euthyroid patients became hypothyroidic under the treatment of sunitinib, but median PFS was not significantly different (18.9 vs 15.9 months)[17]. In our study, we did not find significant differences between the hypothyroidic and euthyroidic patients for PFS and OS. Rate of hypothyroidism is similar to literature and oncologic outcomes of our study was consistent with prospective data which reported previously.

Hyperthyroidism under TKI therapy was not investigated as hypothyroidism, most of the phase trials reported hypothyroidism as side effect, but several case reports had been showed thyrotoxicosis on TKI therapy [18,19]. Jazvic et al. reported a recent study, out of the 62 included patients, hypothyroidism was diagnosed during therapy in 19% and it was preceded by thyrotoxicosis in 3.2% [20]. To our knowledge there is no data investigating oncologic outcomes in patients who developed hyperthyroidism during TKI therapy. We found a significantly higher OS in patients who became hyperthyroidic under TKI therapy. Also, this is an important finding because not only hyperthyroidic patients had longer OS, 50% of THS decreasing patients under TKI had longer OS compared to stayed in normal range. We do not know the possible mechanism or why hyperthyroidism is slightly higher than literature?. One of the possible reason, Turkey has many endemic goiter regions and about 50% of people had thyroid nodules on ultrasound[21,22].

Our study has some major limitations, we cannot have achieved the free thyroid hormone levels and thyroid antibodies to explain possible mechanism, and this is a retrospective study but our findings are new results.

In conclusion, patients who had decreasing TSH levels under the treatment of TKI should have significantly higher overall survival but, hypothyroid patients don't.

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