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Research Article

Hypothyroidism with Sunitinib Therapy and its Correlation with Survival Outcomes in Advanced Renal Cell Carcinoma Patients

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Abstract

Objectives: Hypothyrodism is a common side effect of sunitinib therapy. However, few studies investigated the correlation between SUN induced hypothyroidism and efficacy of sunitinib in metastatic renal cell carcinoma patients(mRCC).

Methods: We retrospectively reviewed 171 mRCC patients who received Sunitinib therapy. Eligibility criteria included receipt of first line therapy with SUN and no known history of hypothyroidism.We investigated the progression free survival and its correlation with SUN induced hypothyroidism.

Results: In a median follow up of 60 months, male gender, current or ex-smoker status, side effect of hypothyroidism after sunitinib use, and palliative radiotherapy treatment were associated with better PFS. Hypothyroidism were not correlated with gender (p=0.222, r=-0.094), smoking status (p=0.343, r=0.076), or palliative radiotherapy (p=0.984, r=-0.002). Median PFS were 13.8 (95% CI: 4.3-19.0) months in hypothyroid (HY) group, and 5.1 (95% CI: 4.6-6.5) months in euthyroid (EU) group (p=0.017). 1y-PFS rates were 52.4% in HY and 17% in EU groups.

In patients with clear cell histology (n=152), median PFS were 13.0 (95% CI: 9.2-16.8) months in HY group, and 5.7 (95% CI: 4.9-6.6) months in EU group (p=0.054). 1y-PFS rates were 52.6% in HY group, and 16.5% in EU group.

Conclusion: Acquired hypothyroidism with sunitinib therapy is consistent with better outcomes in terms of progression free survival.

Keywords: Hypothyroidism, progression free survival, renal cell carcinoma, sunitinib

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Renal cell carcinoma is the most common type of all kidney cancers and accounts for 2-3% of all adult solid malignancies. Over the last decade, treatment for metastatic renal cell carcinoma (mRCC) has transitioned from a non-specific immune approach (in the cytokine era), to the new agents. Targeted therapy with tyrosine kinase ınhibitors (TKIs) against vascular endothelial growth factor (VEGF) is an important option since 2006.[1]

Fatigue, asthenia, anorexia, diarrhea, rash, hand-foot syndrome, hypertension and hypothyrodism are the most common side effects of TKIs. These side effects are generally mild or moderate. However, dose reductions or treatment interruptions occur if side effects cannot be managed properly.

Some of these side effects correlate with prognosis. Rixe et al. reported that hypertension with sunitinib may be a

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predictive factor in mRCC cases.[2] Another study demonstrated better prognosis with on treament neutropenia.[3]

In this study, we evaluated the correlation between hypothyroidism and treatment outcomes. In recent studies, the incidence of hypothyroidism in former euthyroid patients, is around 30-40%, with half of them being subclinical forms.[4]

Methods

Study Design and Patients

In this retrospective analysis, we included patients who received first-line targeted sunitinib therapy for mRCC at two different hospitals between 2008 and 2016. All patients included in this study were at least 18 years of age and had histologically confirmed mRCC.

We obtained demographic, baseline patient characteristics and outcome data retrospectively from the patients' medical charts. Clinical parameters such as gender, age, ECOG performance status, IMDC risk groups,[5] nephrectomy before or after metastasis, histologic subtype (clear cell or other), number of metastatic sites, time duration between diagnosis and treatment <1 year, and presence of any metastases were noted. We divided patients into two groups, those who developed hypothyroidism after the treatment with sunitinib (HY group) and those remained euthyroid after the sunitinib treatment (EU group). 171 were patients included in the final analysis.

Diagnosis

According to the updated NCCN (National Comprehensive Cancer Network) Clinical Practice Guideline for diagnosis, treatment and follow-up of renal cell carcinoma, all patients received multimodality cancer treatments and follow-up at their clinics. The diagnosis of mRCC was based on clinical examination in combination with imaging and was confirmed via pathologic assessment.

Systemic imaging of chest CT with contrast and abdominopelvic CT/MRI with contrast or PET/CT was the standard method for metastasis evaluation and response assessment.

Medical Treatment

The choice of treatment was based on NCCN recommendations. All patients received oral sunitinib 50 mg, once daily, in repeated 6-week cycles of daily use for 4 weeks, followed by 2 weeks of cessation. Palliative radiotherapy (RT) was performed using three-dimensional planning with CT for the relief of painful bone metastases or for uncomplicated bone metastases with a high risk of fracture. Patients who had bone metastases were treated with zoledronic acid to prevent any skeletal-related event every 21-28 days. Toxicity was evaluated using National Cancer Institute Common Toxicity Criteria version 4.0. Physical examination, performance status and laboratory tests were generally assessed on days 0, 15, 45, 75, and 105. Response to therapy was assessed using RECIST criteria every three cycles by systemic imaging.

Definition of Hypothyroidism

Subclinical hypothyroidism was recognised as serum TSH level above the upper limit of normal, with total triiodothyronine (T3) and thyroxine (T4) levels within normal limits (in accordance with guidelines of the ATA American Thyroid Association and the American Association of Clinical Endocrinologists).[6]

Clinical hypothyroidism was determined as low serum T3 and T4 levels together with an elevated TSH level. Patients with hypothyroidism and those with symptoms compatible with hypothyroidism received thyroid hormone replacement treatment with l-thyroxine.

Statistics

Progression-free survival (PFS) was defined as the time from the beginning of first-line targeted therapy to progression, death, cessation of treatment, or to last follow-up. Objective response rate (ORR) was calculated as the sum of the percentage of patients with partial and complete responses on two consecutive, four weeks apart tumor assessments.The characteristics of both groups in frequency tables were analyzed using X^2 and Mann-Whitney U tests (whichever was appropriate). Estimation of the PFS in the univariate analyses was calculated according to the Kaplan-Meier method, and statistical differences between curves were calculated using the Log-rank test.

A p value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp. Released 2010). This study protocol was approved by the Clinical Research Ethics Committee of the University of Health Sciences Umraniye Training and Research Hospital, Istanbul. All the procedures in the report have been in accordance with the ethical principles of the Institutional Research Committee, the 1964 Helsinki declaration, and the subsequent amendments.

Results

Patients Characteristics

171 patients were included in the final analysis. The median patient age was 60 months (95% CI: 58-62) and the median follow-up duration was 23.5 months (95% CI: 18.2-27.2).

Group1 vs Group2

Both groups were similar regarding patient characteristics, disease characteristics, and treatments (Tables 1 and 2).

Response Rates

ORR was 28.5% (complete response rate: 9.5%) in the HY group, however, in the EU group it was 14.6% (complete response rate: 1.3%) (p=0.106).

Survival Analyses

In survival analyses, male gender, current or ex-smoker status, side effects of hypothyroidism after sunitinib use, and palliative radiotherapy treatment were associated with better PFS (Table 3). Hypothyroidism was not correlated with gender (p=0.222, r=-0.094), smoking status (p=0.343, r=0.076), or palliative radiotherapy (p=0.984, r=-0.002). Median PFS was 13.8 months (95% CI: 4.3-19.0) in the HY

Table 1. Patients' characteristics according to groups

	(EU) Euthyroid n (%)	(HY) Hypothyroid n (%)	p
Gender			
Male	118 (78.7)	14 (66.7)	0.219
Female	32 (21.3)	7 (33.3)	
ECOG performance status			
0	97 (64.7)	15 (71.4)	0.885
1	39 (26)	5 (23.8)	
2	13 (8.7)	1 (4.8)	
3-4	1 (0.7)	0	
Nephrectomy*			
Yes	129 (86.0)	20 (95.2)	0.236
No	21 (14.0)	1 (4.8)	
Histologic subtype			
Clear cell	133 (87.5)	19 (90.5)	0.902
Other	11 (7.2)	1 (4.8)	
Unknown	8 (5.3)	1 (4.8)	
Fuhrman grade			
I	2 (1.3)	0	0.817
II	56 (37.3)	9 (42.9)	
III	55 (36.7)	7 (33.3)	
IV	24 (16.0)	5 (23.8)	
Sarcomatoid differentiation			
Yes	36 (24.0)	7 (33.3)	0.461
No	104 (69.3)	14 (66.7)	
IMDC risk classification			
Good	19 (12.7)	4 (19.0)	0.629
Intermediate	97 (64.7)	14 (66.7)	
Poor	31 (20.7)	3 (14.3)	
No. of metastases at presentation			
1	76 (50.7)	8 (38.1)	0.140
2	50 (33.3)	12 (57.1)	
3	13 (8.7)	0	
>4	11 (7.3)	1 (4.8)	
Metastasis sites at presentation			
Lung	69 (46.0)	13 (61.9)	0.627
Bone	45 (30.0)	5 (23.8)	
Brain	17 (11.3)	3 (14.3)	
Liver	5 (3.3)	0	
Palliative RT			
Yes	79 (52.7)	11 (52.4)	0.983
No	64 (42.7)	9 (42.9)	

IMDC: international metastatic renal cell carcinoma database consortium; TKI: tyrosine kinase ınhibitor; RT: radiotherapy before or after metastasis.

Table 2. Patient characteristics according to groups.

Continuous variables	EU group	HY group	p (Mann-Whitney U test)
Age at diagnosis (Mean±SD)	58.3±10.2	59.6±13.1	0.981
BMI at diagnosis (Mean±SD)	26.08±4.58	25.41±3.01	0.686
Median F/U (95% CI) in mos	20.6 (17.3-27.0)	38.2 (21.4-43.6)	0.045
Median PFS (95% CI) in mos	5.1 (4.6-6.5)	13.8 (4.3-19.0)	0.017
Median OS (95% CI) in mos	11.4 (9.2-13.7)	18.7 (8.4-27.8)	0.152

SD: standard deviation; BMI: body mass index as kg/m²); F/U: follow-up duration; mos: months.

group, and 5.1 months (95% CI: 4.6-6.5) in the EU group (p=0.017) (Fig. 1). One-year PFS rates were 52.4% in the HY and 17.3% in the EU groups, respectively. Median OS was 18.7 months (8.4-27.8) in HY group and 11.4 months (9.2-13.7) in the EU group (p=0.152).

In patients with clear cell histology (n=152), median PFS was 13.0 months (95% CI: 9.2-16.8) in the HY group, and 5.7 months (95% CI: 4.9-6.6) in the EU group (p=0.054). One-year PFS rates were 52.6% in the HY group and 16.5% in the EU group.

Discussion

The molecular mechanisms of TKI-induced hypothyroidism are still unclear. Some hypothesized mechanisms are blockage of iodine uptake or inhibition of thyroid peroxidase enzyme activity.[7] Formerly, these hypotheses were thought to be immune-related. Ozao-Choy et al demonstrated that

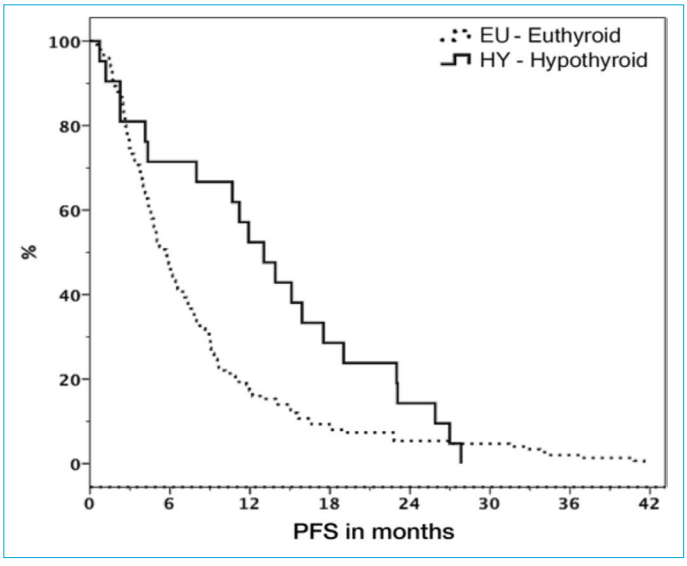

Figure 1. Kaplan Meier Curves for Progression Free Survival: mPFS were 13.8 (95% CI: 4.3-19.0) months in HY, and 5.1 (95% CI: 4.6-6.5) months in EU groups, respectively (p=0.017).

mPFS: median progression-free survival; CI: confidence interval; HY: hypothyroid; EU: euthyroid.

sunitinib can enhance immune response by modulating the tumor microenvironment and interferon (IFN)-gamma expression which may facilitate the activation of Tcells and the mediation of T-helper type 1 cells.[8] However, many studies opposed this hypothesis that no thyroid antibodies were detected in druginduced hypothyroid patients.[9] Some other hypotheses are direct toxicity to thyroid gland, inhibition of iodine uptake or inhibition of thyroid peroxidase enzyme activity. Another plausable theory is TKIs affect vascular endothelial growth factor receptor tyrosine kinase inhibition on thyroid cells which lead to diminished gland vasculature.[10]

Hypothyroidism is a common adverse effect associated with sunitinib and other agents of this class. An incidence analysis covering 24 eligible trials with 6678 sunitinib-treated patients from all treated with sunitinib reported an incidence of all-grade hypothyroidism of 9.8% (95% CI 7.3-12.4%).[11] A meta-analysis covering more than 2700 patients showed a relative-risk for all-grade hypothyroidism of 14.0 ($p < 0.001$). Motzer et al reported in the COMPARZ trial that 24% of mRCC patients acquired hypothyroidism with sunitinib, where as this was 12% with pazopanib.[12] The incidence of acquired hypothyroidism in our study was 12.3%, which is consistent with the literature.

Our study demonstrated that hypothyroidism during sunitinib therapy is consistent with better treatment outcomes. There was a significant difference in median PFS between the patients who developed hypothyroidism on treatment and those who did not (13.8 vs 5.1 months, p=0.017). However, median OS did not differ between groups (18.7 vs 11.4 months, p=0.152). This result could be attributed to treatment heterogeneity after first-line sunitinib therapy.

Furthermore, numerically superior but not statistically significant results may have been impacted by sample size.

Clemons et al study showed that development hypothyroidism during sunitinib or sorafenib therapy correlates with statistically significant better PFS, which supported our results (20 vs 6 months, p=0.02).[13]

Table 3. Survival analysis of patients

Variables	n (%)	One-year PFS (%)	Univariate, p
Gender			
Male	132 (77.2)	25.8	0.026
Female	39 (22.8)	7.7	
Smoking status			
Current or ex-Smoker	94 (60.2)	26.6	0.003
never Smoker	62 (39.7)	9.7	
Symptom status			
Symptomatic	135 (78.9)	20.0	0.238
Asymptomatic	36 (21.0)	27.8	
Co-morbidity			
Yes	115 (68.0)	19.1	0.896
No	54 (32.0)	24.1	
IMDC risk score			
Good	23 (13.7)	8.7	0.642
Intermediate	111 (66.1)	23.4	
Poor	34 (20.2)	26.5	
Nephrectomy			
Yes	149 (87.1)	22.1	0.723
No	22 (12.9)	18.2	
Histologic subtype			
Clear cell	150 (89.8)	20.0	0.948
Non-clear cell	8 (4.8)	25.0	
Unknown	9 (5.4)	22.2	
Sarcomatoid differentiation			
Yes	43 (26.7)	25.6	0.624
No	118 (73.3)	21.2	
Grade			
I	2 (1.3)	0	0.057
II	65 (41.1)	21.5	
III	62 (39.2)	21.0	
IV	29 (18.4)	27.6	
No. of metastases			
1	84 (49.1)	20.2	0.316
2	62 (36.3)	25.8	
3	13 (7.6)	7.7	
≥4	12 (7.0)	25.0	
Side-effect of any kind^			
Yes	132 (84.6)	22.7	0.315
No	24 (15.4)	4.2	
Hypothyroidism after TKI*			
Yes (HY group)	21 (12.3)	52.4	0.026
No (EU group)	150 (87.7)	17.3	
Palliative radiotherapy			
Yes	90 (55.2)	14.4	0.049
No	73 (44.8)	28.8	

Kaplan-Meier and Log-Rank test were used for univariate analysis and Cox regression was used for multivariate analysis. PFS: progression-free survival, IMDC: international metastatic renal cell carcinoma database consortium, TKI: tyrosine kinase inhibitor, HY: hypothyroid, EU: euthyroid. ^Grade 1 or more. *Grade 1 or 2.

Another study supporting our results is Schimidinger et al prospective study which assessed the influence of hypothyroidism in patients with mRCC treated with sunitinib or sorafenib.[14] The rate of objective remission and the median duration of survival were significantly correlated with the occurrence of subclinical hypothyroidism (hypothyroid patients vs euthyroid patients: 28.3% vs 3.3%, p<0.001) and not reached vs 13.9 months (p=0.016), respectively.

However, this study differs from our study that enrolled patients having TKIs after progressing on IFN therapy. This situation may have influenced the treatment outcomes.

In 2014, Nearchou et al from Sweden reported in a meta-analysis which included 11 retrospective and prospective studies (involves Clemons' and Schmidinger's also) between 2008-2012 with 500 mRCC patients treated with sunitinib or sorafenib. There was no significant difference in PFS between patients who acquired hypothyroidism during sunitinib treatment and those who did not. OS was longer in patients who developed hypothyroidism during sunitinib therapy compared with patients who did not (hazard ratio [HR] 0.52; p=0.01); however, the authors urged caution in interpreting these results due to the retrospective nature of the study. Furthermore, this analysis was relatively older than recent studies.

In a retrospective study with 81 patients diagnosed with mRCC and treated with sunitinib, the authors reported that the occurrence of hypothyroidism during treatment in patients was significantly associated with longer PFS, OS and better ORR.[15] The median PFS was 10 (95% CI 6.13-13.8) in the euthyroid patients and 17 months (95% CI 9.33–24.6) in the hypothyroid patients (p=0.001). The median OS was 39 months (95% CI 25.4-52.5) in the hypothyroid patients and 20 months (95% CI 14.7–25.2) in the euthyroid patients (p=0.019). ORR was 46.7 vs 13.7% in hypothyroid patients vs euthyroid patients, respectively (p=0.001).

In 2015, Bailey et al. reported a retrospective analysis of 65 patients with mRCC who received TKI treatment.[16] The median OS was significantly longer in hypothyroid patients (TSH>10 mIU/L) than in euthyroid patients (TSH <10 mIU/L) (not reached vs. 21.4 months, p=0.005). In a prospective observational study from Italy, Pani et al evaluated 27 patients with metastatic carcinomas treated with sunitinib. Of the patients 60% became hypothyroid.[17] Anti-TPO levels became detectable in 25% of the patients.

The authors reported that the development of Anti-TPO antibody was associated with a longer PFS (10.8 vs 5.8 months). A year later the authors stated an update and presumed that thyroid dysfunction represents a biomarker of oncological response.[18]

A retrospective study by Song et al with 155 mRCC patients treated with firstline TKIs (sunitinib, pazopanib, sorafenib, famitinib) was published in 2016.[19] 57 patients (36.8 percent) developed hypothyroidism (serum TSH >10 mIU/L). Hypothyroidism was classified as grade I (total triiodothyronine (T3) and thyroxine (T4) within normal limits, asymptomatic and no treatment required), and grade II (symptomatic, thyroid hormone replacement therapy required, affecting instrumental activities of daily living). Median progressionfree survival (mPFS) was 9.1 months for patients with normal thyroid function, 13.7 months with grade I hypothyroidism and 23.8 months with grade II hypothyroidism (p=0.017). The objective response rate for patients with normal thyroid function, grade I and grade II hypothyroidism were 32.7, 54.5 and 70.8%, respectively (p=0.001). The authors stated that the presence of hypothyroidism or hyperlipidemia during the use of TKIs in mRCC patients may be effective predictive factors of response to TKIs.

In another retrospective study that included 70 mRCC patients treated with sunitinib, the authors reported hypothyroidism as sunitinib toxicity and patients on sunitinib treatment for more than 1 year showed favourable prognostic factors for OS.[20] The authors suggested that hypothyroidism is probably the most reliable side effect to predict the outcome of mRCC and is associated with a significant improvement of OS and PFS of sunitinib-related toxicities. The four weeks with two weeks off schedule (4/2) included 4 weeks of 50 mg/day, followed by a 2-week break. In the continuous dosing schedule, patients were allowed to start with a daily dose of 37.5 mg.

A Japanese retrospective study assessed 50 patients diagnosed with mRCC and treated with sunitinib.[21] In 46% of the patients, hypothyroidism was detected. There was a significant association between better tumor response and the incidence of hypothyroidism (p=0.043).

Bilen et al.[22] reported clinical benefit rates (PR + SD >4 months) in 50% in patients with new-onset hypothyroidism vs 34% in patients without hypothyroidism. The authors stated that new-onset hypothyroidism was associated with favorable clinical response in patients who received TKI treatment.

In a 2017 study, Buda-Nowak et al.[23] from Poland assessed 27 patients diagnosed with mRCC. All patients were treated with first-line sunitinib after nephrectomy. The authors perceived that thyroid dysfunction is a predictive factor of PFS. Patients who had developed hypothyroidism had better median PFS to patients with normal thyroid function (95% CI 20.4-36.2 months versus 9.8 months (6.4-13.1 months).

Iacovelli et al reported in a retrospective study that 54.8% of 104 patients with mRCC experienced "cumulative toxicity" (hypertension, hypothyroidism, handfoot syndrome) with sunitinib or pazopanib.[24] In patients who did or did not experience hypothyroidism, OS was 61.2 and 22.4 months, respectively (p=0.001). Patients who experienced hypothyroidism had a median PFS of 21.8 compared with 10.9 months in those who did not (p=0.006).

In 2018, Lechner et al. conducted a retrospective study that included 538 patients with 6 different types of solid cancers.[25] They noted that 40% of patients developed hy-

pothyroidism. The median OS of patients who developed hypothyroidism was significantly longer than in those who remained euthyroid (49.2 months; 95% CI 36.4-56.4 vs. 22.5 months; 95% CI 17.4-27.9; p<0.001).

The authors stated that new thyroid dysfunction with TKI therapy may predict good prognosis and should not necessitate TKI dose reduction or discontinuation. There are several limitations in our study. First, thyroid function test frequency was heterogeneous. Another limitation is the follow-up period. In our investigation, the median follow-up time of 20.6 and 38.2 months may be too short to show the real advantages. Furthermore, there was a significant difference in follow-up durations (p=0.045).

Conclusion

Like many TKI side effects, sunitinib induced hypothyroidism correlates with better prognosis in terms of progression free survival.

Disclosures

Ethics Committee Approval: Ethical approval may not required dependent on the law and the national ethical guidelines of our country and written informed consent was not required for individual patient because of the study's retrosprective nature. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Peer-review: Externally peer-reviewed.

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Authorship Contributions: Concept – İ.Ç., A.Z., D.T.; Design – İ.Ç., A.Z., M.K.; Supervision – D.T., M.Y., M.K.; Materials – İ.Ç., M.Y., A.Z., Ö.D.; Data collection &/or processing – İ.Ç., M.Y., Ö.D.; Analysis and/or interpretation – D.T., M.K., M.Y.; Literature search – İ.Ç., A.Z., Ö.D.; Writing – İ.Ç., A.Z., Ö.D.; Critical review – M.K., M.Y., D.T.

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