Correlation of Degree of Hypothyroidism With Survival Outcomes in Patients With Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors

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Abstract

Hypothyroidism frequently occurs in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs). In the present observational study, the severity of hypothyroidism correlated with improved survival outcomes. Thus, emphasis should be placed on the appropriate management of hypothyroidism, rather than on VEGFR-TKI therapy dose reduction or discontinuation.

Background: Hypothyroidism is a common adverse effect of vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) therapy in patients with metastatic renal cell carcinoma (mRCC). Some studies have shown an association with improved survival. However, hypothyroidism severity has not been correlated with survival outcomes. We report the incidence and severity of VEGFR-TKI therapy-associated hypothyroidism in correlation with the survival outcomes of patients with mRCC. **Patients and Methods:** A retrospective analysis of patients with mRCC who received VEGFR-TKIs (2004 through 2013) was conducted from a single institutional database. Hypothyroidism, progression-free survival (PFS), and overall survival (OS) were assessed. Univariate and multivariate analyses were performed using the Kaplan-Meier method and Cox proportional hazard models. **Results:** Of 125 patients with mRCC, 65 were eligible. Their median age was 59 years (range, 45-79 years), and 46 (70.8%) were male. Hypothyroidism occurred in 25 patients (38.5%), of whom 13 had a peak thyroid-stimulating hormone (TSH) level $>$ 10 mIU/L during treatment. The median OS was significantly longer in patients with a peak TSH $>$ 10 mIU/L than in patients with a peak TSH of $\leq$ 10 mIU/L (not reached vs. 21.4 months, $P = .005$). On multivariate analysis, risk criteria, number of previous therapies, and severe hypothyroidism (TSH $>$ 10 mIU/L) during VEGFR-TKI therapy remained significant for improvements in PFS and OS. **Conclusion:** The severity of VEGFR-TKI therapy-associated hypothyroidism (TSH $>$ 10 mIU/L) was associated with improved survival outcomes in patients with mRCC and should not necessitate a dose reduction or therapy discontinuation.

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Introduction

The advent of targeted therapy with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) has revolutionized the management of metastatic renal cell carcinoma (mRCC). At present, 4 VEGFR-TKIs (sorafenib, sunitinib, pazopanib, and axitinib) have been approved by the US Food and Drug Administration for the treatment of mRCC[1-4] and have been recognized by the consensus guidelines as therapeutic options for predominately clear cell mRCC.[5,6]

Hypothyroidism in association with VEGFR-TKI therapy has been reported in a wide range (7%-85%) of patients with mRCC.[7-16] Although reports of improved survival in patients with mRCC who developed VEGFR-TKI treatment-related hypothyroidism have been inconsistent, the severity of hypothyroidism has not been directly correlated with survival (Table 1).[9-11,17-22] The goal of our study was to evaluate the incidence of hypothyroidism in patients with mRCC treated with VEGFR-TKIs and to correlate its severity with the survival outcomes (Table 1).

Patients and Methods

The present study was a retrospective study of patients with mRCC treated with VEGFR-TKIs from January 1, 2004 to October 31, 2013, with follow-up data available through December 1, 2013. The University of Utah institutional review board (IRB no. 67518) approved the present study. A retrospective review of the electronic medical records was performed, and the following data were collected: patient demographics, Memorial Sloan-Kettering Cancer Center (MSKCC) and International Metastatic RCC Database Consortium (IMDC) or Heng risk criteria, previous and subsequent therapy for mRCC, dates of initiation and discontinuation of VEGFR-TKI therapy, the best responses to VEGFR-TKI therapy, and the reason for discontinuation of VEGFR-TKI therapy. In addition, thyroid function-specific data were collected: history of hypothyroidism, baseline thyroid hormone replacement dose (if applicable), requirement for the initiation of thyroid hormone replacement, requirement for any dose increase, the highest documented dose prescribed, and the serial thyroid-stimulating hormone (TSH) concentrations. Free thyroxine concentrations were not recorded owing to inconsistent ordering patterns among the treating physicians. Only patients with an intact thyroid gland were included, and they were required to have ≥ 2 documented TSH values (at baseline and after VEGFR-TKI therapy initiation or 2 consecutive TSH concentrations during VEGFR-TKI therapy).

Hypothyroidism was defined as any increase in the serum TSH concentration greater than the institutional upper limit of normal (ULN) or increasing TSH concentrations greater than the ULN during VEGFR-TKI therapy. In addition, using the peak TSH concentration, the patients were categorized as having euthyroidism (normal TSH), mild hypothyroidism (TSH greater than the ULN but ≤ 10 mIU/L), or severe hypothyroidism (TSH > 10 mIU/L). Patients with a peak TSH concentration of ≤ 10 mIU/L (combined euthyroidism and mild hypothyroidism) were compared with those with a TSH level > 10 mIU/L (severe hypothyroidism) on univariate analysis. The change in the TSH concentration (TSH_{delta}) from baseline was also calculated ($TSH_{delta} = TSH_{max} - TSH_{baseline}$). When the $TSH_{baseline}$ was greater than the TSH_{max}, a value of 0 was assigned.

Statistical Analysis

Descriptive statistics were used to summarize the patient and treatment characteristics. The Kaplan-Meier method with stratified log-rank tests were used to demonstrate progression-free survival (PFS) and overall survival (OS) by the severity of hypothyroidism (euthyroid vs. mild vs. severe hypothyroidism). Univariate and multivariate analyses were performed using the Kaplan-Meier method and Cox proportional hazard models. The change in TSH from

Table 1 Studies Reporting Correlations of Survival Outcomes With VEGFR-TKI Therapy-Associated Hypothyroidism in Patients With mRCC

Study	VEGR-TKI	Patients[a] (n)	Median PFS With Versus Without Hypothyroidism (mo)	Median OS With Versus Without Hypothyroidism (mo)
Wolter et al,[17] 2008	Sunitinib	40	10.3 versus 3.6[b] ($P = .047$)	18.2 versus 6.6 ($P = .13$)
Bladou et al,[18] 2010	Sunitinib	111	19.1 versus 16.0 ($P = .94$)	NR
Pinto et al,[19] 2010	Sunitinib	28	15.4 versus 9.1 ($P = .566$)	26.6 versus 24.3 ($P = .687$)
Schmidinger et al,[10] 2011	Sunitinib/sorafenib	78[c]/83[d]	17.0 versus 10.8 ($P = .53$)	Not reached versus 13.9[b] ($P = .016$)
Riesenbeck et al,[20] 2011	Sunitinib/sorafenib	83	16.0 versus 6.0[b] ($P = .032$)	NR
Sabatier et al,[9] 2012	Sunitinib	69[e]	18.9 versus 15.9 ($P = .94$)	NR
Sella et al,[21] 2012	Sunitinib	30	12.2 versus 9.45 ($P = .234$)	22.4 versus 13.9 ($P = .2287$)
Baldazzi et al,[22] 2012	Sunitinib	22	8.55 versus 7.03[b] ($P < .05$)	NR
Clemons et al,[11] 2012	Sunitinib/sorafenib	61	18.2 versus 10.1[b] ($P = .01$)	NR
Bailey et al, 2014[f]	Sunitinib/sorafenib/ pazopanib/axitinib	65[f]	47.7 versus 9.3[b] ($P = .009$)	Not reached versus 21.4[b] ($P = .005$)

Abbreviations: NR = not reported; OS = overall survival; PFS = progression free survival; TSH = thyroid-stimulating hormone; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.
[a]Number of evaluable patients.
[b]Statistically significant.
[c]Patients evaluable for PFS analysis within 2 months of treatment.
[d]Patients evaluable for OS analysis within 2 months of treatment.
[e]Patients evaluable using landmark method after 6 months of treatment.
[f]Severe hypothyroidism (TSH > 10 mIU/L) versus combined euthyroidism and mild hypothyroidism (TSH ≤ 10 mIU/L).