Original Article

Hypothyroidism in Patients With Renal Cell Carcinoma

Blessing or Curse?

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BACKGROUND: Sunitinib and sorafenib are tyrosine kinase inhibitors that have important antitumor activity in metastatic renal cell carcinoma (mRCC). Hypothyroidism constitutes a commonly reported side effect of both drugs, and particularly of sunitinib. The objective of this analysis was to investigate whether the occurrence of hypothyroidism during treatment with sunitinib and sorafenib affects the outcome of patients with mRCC. **METHODS:** Eighty-seven consecutive patients with mRCC who were to receive treatment with sunitinib or sorafenib were included in a prospective analysis. Thyroid function was assessed in each patient every 4 weeks during the first 2 months of treatment and every 2 to 4 months thereafter. Assessment included serum levels of thyroid-stimulating hormone (TSH), tri-iodthyronine (T3), and thyroxine (T4). Subclinical hypothyroidism was defined as an increase in TSH above the upper limit of normal (>3.77 μM/mL) with normal T3 and T4 levels. **RESULTS:** Subclinical hypothyroidism was evident in 5 patients at baseline and occurred in 30 patients (36.1%) within the first 2 months after treatment initiation. There was a statistically significant correlation between the occurrence of subclinical hypothyroidism during treatment and the rate of objective remission (hypothyroid patients vs euthyroid patients: 28.3% vs 3.3%, respectively; $P < .001$) and the median duration of survival (not reached vs 13.9 months, respectively; hazard ratio, 0.35; 95% confidence interval, 0.14-0.85; $P = .016$). In multivariate analysis, the development of subclinical hypothyroidism was identified as an independent predictor of survival (hazard ratio, 0.31; $P = .014$). **CONCLUSIONS:** The current results indicated that hypothyroidism may serve as a predictive marker of treatment outcome in patients with mRCC. Thus, the interpretation of hypothyroidism during treatment with sunitinib and sorafenib as an unwanted side effect should be reconsidered. *Cancer* **2010;116:000–000.** © *2010 American Cancer Society.*

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Antiangiogenic agents have led to clinically meaningful advances in the treatment of patients with metastatic renal cell carcinoma (mRCC). Among these novel therapeutic agents, the tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib were the first to be approved for the treatment of mRCC. Both inhibit tyrosine kinases of growth factor receptors, the most important of which are the vascular endothelial growth factor receptor (VEGFR), the platelet-derived growth factor receptor (PDGFR), the stem cell factor KIT receptor (a cytokine receptor), the fms-like tyrosine kinase 3 (FLT3) receptor, and the protein product of the ret oncogene.[1,2] Compared with interferon-alpha, first-line treatment with sunitinib reportedly improved the objective remission rate (ORR) significantly (31% vs 6%; $P < .001$) along with progression-free survival (PFS) (11 months vs 5 months; $P < .001$).[3] On the basis of these findings, sunitinib has been considered the new standard first-line treatment in mRCC. Sorafenib, apart from being a VEGFR TKI and a PDGFR TKI, also inhibits RAF, an important member of the RAS-RAF-MEK-ERK signaling pathway. Signal transduction mediated by this pathway is important for tumor progression.[4] In patients who fail on immunotherapy, sorafenib reportedly

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provided a statistically significant benefit in PFS compared with placebo (5.5 months and 2.8 months, respectively; $P < .01$).[5] Thus, sorafenib is the recommended standard of care in this patient population.[6]

Common toxicities reported from these agents are hand-foot syndrome, diarrhea, stomatitis, hypertension, and fatigue.[3,5,7,8] These observations have been made in patients with RCC and in patients with gastrointestinal stroma tumors. The frequency of patient-reported fatigue prompted several investigators to monitor thyroid function in these patients to rule out hypothyroidism. Both sunitinib and sorafenib reportedly induced subclinical or overt hypothyroidism in up to 85% and 21% of patients, respectively.[3,9-11] The mechanism through which these TKIs cause changes in thyroid function is not entirely understood. Explanations include TKI-induced inhibition of VEGFR tyrosine kinases on thyroid cells, resulting in capillary regression[12,13]; inhibition of the protein product of the ret proto-oncogene[14]; and inhibition of iodine uptake[15] or of peroxidase activity.[16] Finally, the kinases that are inhibited by sunitinib and sorafenib regulate growth and function in both normal and neoplastic thyroid cells.[17] Thus, it has been demonstrated that these agents induce clinical responses in patients with thyroid carcinoma.[18]

Drug-induced hypothyroidism may not necessarily be perceived as an unwanted, detrimental toxicity. Thyroid hormones reportedly increased the growth of glioma cells,[19] whereas hypothyroidism inhibited the growth of lung, prostate, hepatocellular, and mammary tumors in animal models.[20-22] Hypothyroidism was associated with improved outcomes in patients with head and neck cancer,[23] glioblastoma,[24] and metastatic breast cancer.[25] In patients with mRCC, the association between hypothyroidism and survival has been controversial: High thyroid-stimulating hormone (TSH) levels before treatment with interleukin-2 were associated with poor survival,[26] whereas the therapeutic induction of hypothyroidism reportedly favored a response to interleukin-2 treatment.[27]

Reports of sunitinib with induced and sorafenib-induced hypothyroidism in patients mRCC were consistent with our own observations and prompted us to establish the regular monitoring of thyroid function in all patients who were receiving either drug. The objective of the current prospective, explorative study was to investigate whether hypothyroidism has an impact on the outcome of patients with mRCC who receive sunitinib or sorafenib.

MATERIALS AND METHODS

Patients

Eighty-seven consecutive patients who were considered for treatment with a TKI for mRCC were included in this exploratory study. These patients had either progressed on cytokines and/or had received a TKI or monoclonal antibody before the current analysis was initiated. The choice to prescribe sunitinib or sorafenib was based on the availability of each agent and, subsequently, on the results from the pivotal trials.[3]

Sunitinib or sorafenib was prescribed at a dose of 50 mg daily (on a 4 weeks on/2 weeks off schedule) or 800 mg daily (continuously), respectively. Staging investigations were performed at baseline and every 12 weeks thereafter and included computed tomography scans and/or magnetic resonance imaging as indicated. Objective remission was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST).[28]

Blood cell counts and serum chemistry were assessed at baseline, every 2 weeks during the first 3 months of treatment, and once monthly thereafter. Thyroid function was assessed at baseline, monthly during the first 2 months of treatment, and every 2 to 4 months thereafter and included serum levels of TSH and the thyroid hormones tri-iodthyronine (T3) and thyroxine (T4). Before treatment, all patients were analyzed for the presence or history of thyroid dysfunction. According to our institutional laboratory, the following serum levels related to thyroid function were considered normal: TSH, from 0.44 to 3.77 μU/mL; T4, from 58 to 124 ng/mL; and T3, from 0.8 to 1.8 ng/mL. Subclinical hypothyroidism was defined as TSH serum levels above the upper limit of normal with normal T4 and T3 serum concentrations.[29]

Clinical symptoms were assessed every 2 weeks during the first 3 months of treatment and once monthly thereafter. Thyroid hormone replacement with levothyroxine was initiated based on the intensity of clinical symptoms reported by the patient. An informed consent was not required; because, after the first reported occurrence of hypothyroidism in patients who were receiving sunitinib or sorafenib, a thyroid function assessment was considered part of the routine test battery in our department. The institutional ethics committee provided written approval for this procedure and agreed on publication of the data.

Statistical Methods

Progression-free survival (PFS) was computed as the time from treatment initiation to disease progression or death,

and overall survival (OS) was computed as the time from treatment initiation to death. Survival to the end of the observation period was considered a censored observation. To model a possible time-dependent effect of an early TSH increase (>3.77 μM/mL), survival analyses were performed with different starting times: at the initiation of therapy, 1 month after therapy initiation, and 2 months after therapy initiation (eg, for the latter starting time, only those patients who were observed for at least 2 months were included). This analysis strategy allowed us to use common Kaplan-Meier curves in a time-dependent manner. All reported survival times were computed from the date therapy was initiated. Log-rank tests and Cox proportional hazards models were used for univariate and multiple assessments of prognostic factors. A 2-tailed significance level of 5% was assumed. Because the study was exploratory rather than confirmatory, no adjustment for multiple testing was done.

RESULTS

Patient Characteristics

The baseline characteristics of all patients are presented in Table 1. Between August 2006 and September 2008, 87 consecutive patients with a median age of 64 years were included in this analysis. Of these, 82.8% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and most (71.3%) were classified with intermediate-risk disease according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk group assessment.[30] Previous treatments included cytokines (63.2% of patients) and TKIs (sunitinib, 13.8%; sorafenib, 10.3%; and/or bevacizumab, 9.2%), and 5.7% of patients also had undergone (incomplete) metastasectomy before treatment.

Thyroid Function at Baseline

Seventy-eight of 87 patients were evaluable for thyroid function assessment at baseline. Fourteen patients had a history of hypothyroidism with associated levothyroxine treatment. TSH levels at baseline (TSH_0) were below or above the normal range in 4 patients (4.6%) and 5 patients (5.7%), respectively. No association was observed between the type of previous treatment and TSH_0 levels ($P = .16$; chi-square statistic, 2.3).

Thyroid Function During the Course of Treatment With Sunitinib and Sorafenib

All patients were evaluable for thyroid function during treatment. Data on thyroid function assessments during

Table 1. Baseline Demographics and Clinical Characteristics

Variable	No. of Patients (%)
All patients	87 (100)
Sex	
Men	56 (64.4)
Women	31 (35.6)
Median age, y [range]	64.2 [44-86]
ECOG PS	
0	72 (82.8)
1	10 (11.5)
2	3 (3.4)
3	2 (2.3)
Nephrectomy	85 (97.7)
Time from primary tumor to metastases	
<1 y	45 (51.7)
>1 y	42 (48.3)
MSKCC risk group	
Favorable risk	20 (23)
Intermediate risk	62 (71.3)
Poor risk	5 (5.7)
Treatment before TKI evaluated for thyroid function	
Cytokine-based	55 (63.2)
Sunitinib: Median treatment duration, 5 mo	12 (13.8)
Sorafenib: Median treatment duration, 6.2 mo	9 (10.3)
Bevacizumab	8 (9.2)
No. of metastatic sites	
1	26 (29.9)
2	38 (43.7)
≥3	23 (26.4)
Location of metastatic sites	
Lung	60 (69)
Liver	15 (17.2)
Bone	33 (37.9)
Lymph node	29 (33.3)
CNS	6 (6.9)
Other	36 (41.4)
No. of patients evaluable for thyroid function tests	87/87 (100)
History of hypothyroidism with levothyroxine treatment	14 (16.1)
History of thyroiditis: Hashimoto or cytokine-induced	2 (2.3)
History of hyperthyroidism: Thiamazole treatment	1 (1.1)
Baseline TSH, > or < normal range	
<0.44 μU/mL	5 (5.7)
>3.77 μU/mL	4 (4.6)
Baseline T3, > or < normal range	
<0.8 ng/mL	5 (5.7)
>1.8 ng/mL	2 (2.3)
Baseline T4, > or < normal range	
<58 ng/mL	3 (3.4)
>124 ng/mL	1 (1.1)

ECOG PS indicates Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; TKI, tyrosine kinase inhibitor; CNS, central nervous system; TSH, thyroid-stimulating hormone; T3, tri-iodothyronine; T4, thyroxine.

TKI treatment and clinical outcomes are presented in Tables 2, 3, and 4. Increases in TSH >3.77 μM/mL within the first month (TSH_{max1}) and within 2 months (TSH_{max2}) of treatment were observed in 30.5% of patients (sunitinib, n = 9; sorafenib, n = 16) and 36.1% of patients (sunitinib, n = 12; sorafenib, n = 18), respectively, whereas T4 and T3 concentrations were within normal ranges during the entire treatment period. The diagnosis of hypothyroidism was associated with fatigue in 21 patients. Hormone replacement was initiated in 16 patients and led to TSH normalization in 4 patients, whereas 12 patients remained hypothyroid, although they had lower TSH levels than before they received hormone replacement. Seven patients who were treated for hypothyroidism before they started treatment with sunitinib or sorafenib required an increase in their levothyroxine dose. Treatment with levothyroxine did not alter the incidence or severity of fatigue. The incidence of fatigue in hypothyroid and euthyroid patients was 70% and 58.5%, respectively. No statistically significant difference was observed in the incidence of fatigue (chi-square statistic, 1.08; $P = .35$) or the severity of fatigue (chi-square statistic, 0.329; $P = .55$) between those 2 groups.

No statistically significant association was observed between the occurrence of hypothyroidism and previous treatment (chi-square statistic, 1.604; $P = .21$) and the dose or schedule of sunitinib or sorafenib (chi-square statistic, 1.66; $P = .255$). Moreover, we observed no association between the development of hypothyroidism and patient age and or sex (patients ages 18-49 years vs patients aged ≥50 years: chi-square statistic, 0.19; $P = 1.00$; patients aged <80 years vs patients aged ≥80 years: chi-square statistic, 0.034; $P = 1.00$) or between the development of hypothyroidism in men and women (chi-square statistic, 3.908; $P = .06$).

Table 2. Thyroid-Stimulating Hormone Levels at Baseline and During the First and Second Months of Treatment: Response to Treatment

Variable	No. of Patients (%)	
	All Patients	Patients With TSH >3.77 μM/mL
Patients evaluable for thyroid function during treatment	87 (100)	54 (62.1)
Patients evaluable for thyroid function at baseline		
All patients	78 (89.7)	5 (6.4)
Sunitinib group	41	2 (4.9)
Sorafenib group	37	3 (8.1)
Patients evaluable for TSH during first mo		
All patients	82 (94.3)	25 (30.5)
Sunitinib group	44	9 (20.5)
Sorafenib group	38	16 (42.1)
Patients evaluable for TSH during second mo		
All patients	83 (95.4)	30 (36.1)
Sunitinib group	44	12 (27.3)
Sorafenib group	39	18 (46.2)
Median TSH levels in patients with hypothyroidism [range], μM/mL[a]		
First mo		5.1 [3.8-23.0]
Second mo		5.8 [4.1-23.0]

TSH indicates thyroid-stimulating hormone.
[a] Hyperthyroidism was defined as a TSH level >3.77 μM/mL

Table 3. Objective Remission According to Response Evaluation Criteria in Solid Tumors Based on Increased Thyroid-Stimulating Hormone Levels at Any Time During Treatment (n = 83)

Patient Group	No. of Responses				
	PR/CR	SD	PD	ORR, %	*P*[a]
All patients (n=83 evaluable)	16	46	21	19.3	
With TSH >3.77 μM/mL (n=53 evaluable)	15	31	7	28.3	<.001
Without TSH >3.77 μM/mL (n=30 evaluable)	1	15	14	3.3	
Sunitinib group					
With TSH >3.77 μM/mL (n=32 evaluable)	11	16	5	34.4	.010
Without TSH >3.77 μM/mL (n=13 evaluable)	0	8	5	0	
Sorafenib group					
With TSH >3.77 μM/mL (n=21 evaluable)	4	15	2	19	.006
Without TSH >3.77 μM/mL (n=17 evaluable)	1	7	9	5.9	

PR indicates partial remission; CR, complete remission; SD, stable disease; PD, progressive disease; ORR, objective remission rate; TSH, thyroid-stimulating hormone.
[a] *P* values were based on the exact Wilcoxon rank-sum test.

Table 4. Progression-Free Survival, Overall Survival, and Outcome According to Thyroid-Stimulating Hormone Levels Within the First and Second Months of Treatment

Patients Evaluable for PFS/OS	Median PFS (95%CI), mo	HR (95%CI), mo[a]	P[a]	Median OS (95%CI), mo	HR (95%CI), mo[a]	P[a]
All patients, n = 86/n = 87	11.4 (7.0-14.9)			25.4 (13.9-NR)	—	—
Sunitinib group, n = 47/n = 48	11.1 (6.5-17.0)	0.85 (0.50-1.43)	.54	25.4 (13.4-NR)	0.99 (0.50-1.94)	.97
Sorafenib group, n = 39/n = 39	11.5 (5.3-15.9)	1.00		NR (11.4-NR)	1.00	
Outcome of evaluable patients with a TSH_{max1} increase >3.77 μM/mL, n = 79/n = 82						
All TSH_{max1} >3.77 μM/mL (24/25)	17.0 (11.4-20.4)	0.71 (0.38-1.34)	.29	NR (NR-NR)	0.39 (0.15-1.01)	.044
All TSH_{max1} ≤3.77 μM/mL, n = 55/n = 57	10.4 (6.4-13.9)	1.00		14.1 (12.5-NR)	1.00	
Sunitinib group			.86			.56
TSH_{max1} >3.77 μM/mL, n = 8/n = 9	11.8 (4.9-17.0)	1.10 (0.38-3.2)		NR (5.9-NR)	1.46 (0.41-5.1)	
TSH_{max1} ≤3.77 μM/mL, n = 34/n = 35	10.8 (6.6-17.0)	1.00		25.4 (13.4-NR)	1.00	
Sorafenib group						
TSH_{max1} >3.77 μM/mL, n = 16/n = 16	19.3 (11.4-22.1)	0.46 (0.20-1.07)	.065	NR (NR-NR)	0.15 (0.03-0.67)	.004
TSH_{max1} ≤3.77 μM/mL, n = 21/n = 22	5.5 (4.2-13.9)	1.00		13.7 (5.8-NR)	1.00	
Outcome of patients with a TSH_{max2} increase >3.77μM/mL, n = 78/n = 83						
All TSH_{max2} >3.77 μM/mL, n = 28/n = 30	17.0 (7.6-19.8)	0.83 (0.47-1.48)	.53	NR (NR-NR)	0.35 (0.14-0.85)	.016
All TSH_{max2} ≤3.77 μM/mL, n = 50/n = 53	10.8 (6.4-13.9)	1.00		13.9 (12.2-NR)	1.00	
Sunitinib group						
TSH_{max2} >3.77 μM/mL, n = 11/n = 12	11.8 (4.9-19.8)	1.25 (0.54-2.9)	.60	NR (6.2-NR)	0.68 (0.19-2.4)	.54
TSH_{max2} ≤3.77 μM/mL, n = 30/n = 32	10.8 (6.5-17.0)	1.00		18.3 (12.5-NR)	1.00	
Sorafenib group						
TSH_{max2} >3.77 μM/mL, n = 17/n = 18	17.5 (7.0-22.1)	0.53 (0.23-1.20)	.12	NR (NR-NR)	0.21 (0.06-0.73)	.007
TSH_{max2} ≤3.77 μM/mL, n = 20/n = 21	7.1 (4.4-13.9)	1.00		12.2 (5.8-NR)	1.00	

PFS indicates progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; NR, not reached; TSH_{max1}, highest TSH level >3.77 μM/mL measured within the first month after initiating treatment; TSH_{max2}, highest TSH level >3.77 μM/mL measured within the first 2 months after initiating treatment

[a] Univariate *P* values were based on the log-rank test, and CIs for univariate hazard ratios were based on normal approximation from a Cox model.

Remissions

Eleven patients who were receiving sunitinib and 5 patients who were receiving sorafenib achieved either complete remission (n = 3) or partial remission (n = 8), for an ORR of 19.3%, as outlined in Tables 2 and 3. Fifteen of those 16 patients were diagnosed with (subclinical) hypothyroidism during sunitinib or sorafenib treatment. There was a statistically significant correlation between the occurrence of hypothyroidism and the achievement of remission (ORR: hypothyroid patients, 28.3%; euthyroid patients, 3.3%; $P < .001$).

Progression-Free Survival

The median PFS was 11.4 months (95% confidence interval [CI], 7.0-14.9 months), as outlined in Table 4. Patients who had a TSH_{max1} >3.77 μM/mL had a longer PFS (17.0 months) than patients who had a TSH_{max1} ≤3.77 μM/mL (10.4 months; $P = .29$; hazard ratio [HR], 0.71). The impact of hypothyroidism on PFS was particularly pronounced in the sorafenib treatment group (TSH_{max1} >3.77 μM/mL: PFS, 19.3 months; TSH_{max1} ≤3.77 μM/mL: PFS, 5.5 months; HR, 0.46; 95% CI, 0.20-1.07; $P = .065$). A similar difference was observed for patients who had a TSH_{max2} >3.77 μM/mL compared with patients who had a TSH_{max2} ≤3.77 μM/mL (entire cohort: PFS, 17 months and 10.8 months, respectively; HR, 0.83; 95% CI, 0.47-1.48; $P = .53$; sorafenib treatment group: 17.5 months and 7.1 months, respectively; HR, 0.53; 95% CI, 0.23-1.20; $P = .12$.

Overall Survival

The median OS was 25.4 months (95% CI, 13.9 months to not reached) for the entire patient population, 25.4 months for patients in the sunitinib treatment group, and not reached for patients in the sorafenib treatment group.

Patients with hypothyroidism at baseline survived longer than patients without hypothyroidism at baseline (Fig. 1a). Patients who had hypothyroidism within the first month of treatment (TSH_{max1}) had a statistically significant longer survival than patients who had normal

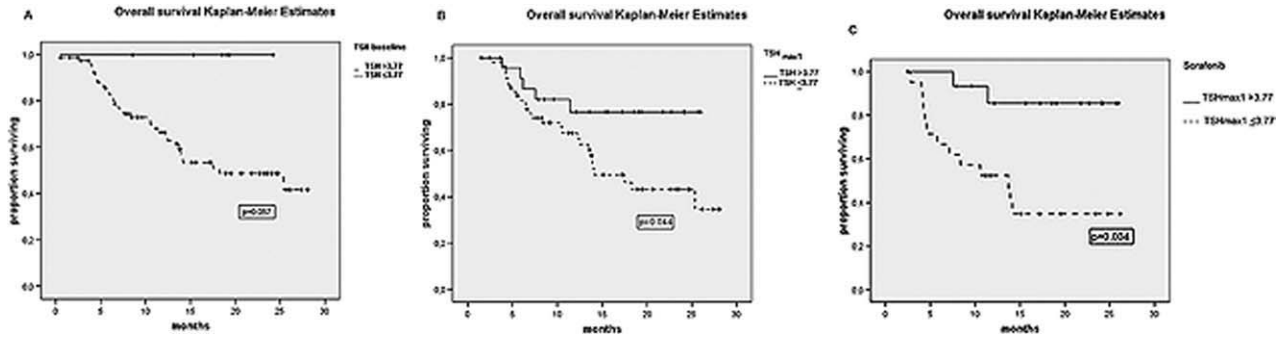

Figure 1. Survival is illustrated based on the level of thyroid-stimulating hormone (TSH) at baseline (TSH_{max0}) and within the first month of treatment (TSH_{max1}) in (a) all patients who had hypothyroidism at baseline versus patients without baseline hypothyroidism (not reached and 18.3 months, respectively; hazard ratio [HR], 0.42; $P = .057$), (b) all patients who had a TSH_{max1} >3.77 μM/mL versus all patients who had a TSH_{max1} ≤3.77 μM/mL (not reached and 14.1 months, respectively; HR, 0.39; $P = .044$), and (c) patients in the sorafenib treatment group who had a TSH_{max1} >3.77 μM/mL versus patients in the sorafenib treatment group who had a TSH_{max1} ≤3.77 μM/mL (not reached and 13.7 months, respectively; HR, 0.15; $P = .004$).

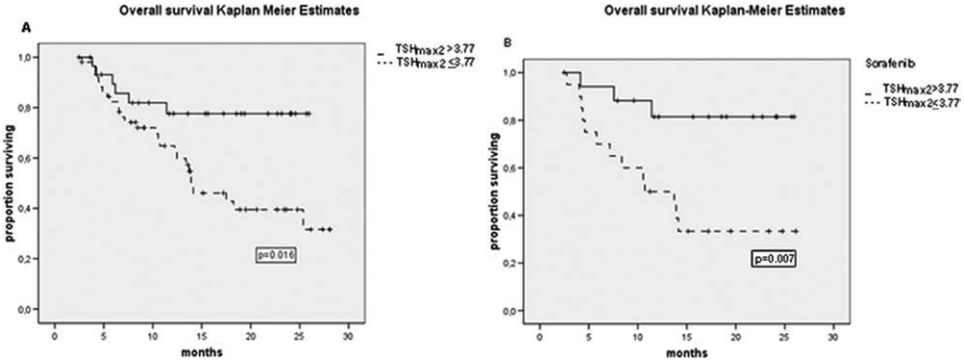

Figure 2. Survival is illustrated based on the level of thyroid-stimulating hormone (TSH) within 2 months of treatment (TSH_{max2}) in (a) all patients who had a TSH_{max2} >3.77 μM/mL versus all patients who had a TSH_{max2} ≤3.77 μM/mL (not reached and 13.9 months, respectively; hazard ratio [HR], 0.35; $P = .016$) and (b) patients in the sorafenib treatment group who had a TSH_{max2} >3.77 μM/mL versus patients in the sorafenib treatment group who had a TSH_{max2} ≤3.77 μM/mL (not reached and 12.2 months, respectively; HR, 0.21; $P = .007$).

TSH_{max1} levels (not reached and 14.1 months, respectively; HR, 0.39; 95% CI, 0.15-1.01; $P = .044$) (Fig. 1b). Similar results were obtained when we analyzed the impact of increased TSH within 2 months of treatment on survival for the entire cohort (TSH_{max2} >3.77 μM/mL vs ≤3.77 μM/mL: not reached and 13.9 months, respectively; HR, 0.35; 95% CI, 0.14-0.85; $P = .016$ (Fig. 2a). These results were particularly pronounced in the subgroup of patients who received sorafenib: TSH_{max1} (>3.77 μM/mL vs ≤3.77 μM/mL: not reached and 13.7 months; HR, 0.15; 95% CI, 0.03-0.67; $P = .004$) (Fig. 1c); TSH_{max2} (>3.77 μM/mL vs ≤3.77 μM/mL: not reached and 12.2 months, respectively; HR, 0.21; 95% CI, 0.06-0.73; $P = .007$) (Fig. 2b).

Hypothyroidism as a Predictor of Progression-Free Survival and Overall Survival

Several clinical and laboratory variables were tested for their impact on PFS (Table 5) and OS (Table 6), including the time from diagnosis to the development of metastatic disease (<1 year or ≥1 year), ECOG performance status (0 vs ≥1), the number of metastatic sites (1 vs 2 vs ≥3), the types of metastatic sites (lung, liver, bone, central nervous system), types of previous treatments (cytokines, anti-VEGF-based) MSKCC risk group, TSH_0 (>3.77 μM/mL or ≤3.77 μM/mL), TSH_{max1} (>3.77 μM/mL or ≤3.77 μM/mL), and TSH_{max2} (>3.77 μM/mL or ≤3.77 μM/mL). None of these factors were associated with PFS

Table 5. Univariate and Multivariate Analyses of Progression-Free Survival

Variable	No. of Patients	Median PFS (95%CI), mo	Log-Rank *P*
Baseline Univariate Analysis: PFS			
Time from diagnosis to treatment			**.61**
≤1 y	45	10.8 (5.5-14.9)	
>1 y	41	11.8 (6.5-20.4)	
ECOG PS			**.14**
0	71	11.8 (7.0-15.9)	
≥1	15	7.1 (5.6-15.1)	
No. of metastatic sites			**.12**
1	26	13.8 (5.6-NR)	
>1	60	10.8 (6.5-13.9)	
Metastatic site lung			**.71**
Yes	60	11.5 (7.0-15.1)	
No	26	10.4 (5.3-22.1)	
Metastatic site liver			**.28**
Yes	15	11.4 (5.3-13.9)	
No	71	11.1 (6.6-17.0)	
Metastatic site bone			**.26**
Yes	33	6.6 (4.7-17.0)	
No	53	12.2 (9.5-15.9)	
Metastatic site CNS			**.14**
Yes	6	9.2 (4.1-11.1)	
No	80	11.8 (6.6-15.9)	
MSKCC risk group			**.35**[a]
Favorable	19	11. 8 (7.0-NR)	
Intermediate	62	10.8 (5.6-14.9)	
Poor	5	15.9 (2.9-20.7)	
TSH_0, μM/mL			**.14**
>3.77	5	NR (11.8-NR)	
≤3.77	72	10.8 (6.5-13.9)	
Prior treatment cytokines			**.45**
Yes	55	11.4 (7.0-15.9)	
No	31	13.1 (4.5-17.5)	
Prior treatment anti-VEGF based			**0.26**
Yes	24	11.5 (4.9-15.9)	
No	62	11.1 (6.5-17.0)	

Variable	Variable category[b]	HR	*P*
Multivariate Analyses: PFS			
PFS and TSH_{max1}, n = 79 evaluable patients			
Time from diagnosis to treatment	≤1 y vs >1 y	0.78	.43
ECOG PS	0 vs ≥1	1.54	.26
No. of metastatic sites	1 vs >1	1.18	.67
MSKCC risk group	Favorable vs intermediate vs poor	1.14	.68[a]
Treatment	Sorafenib vs sunitinib	0.73	.32
TSH_{max1}, μM/mL	≤3.77 vs >3.77	0.77	.52
PFS and TSH_{max2}, n = 78 evaluable patients			
Time from diagnosis to treatment	≤1 y vs >1 y	0.72	.33
ECOG PS	0 vs ≥1	1.64	.18
No. of metastatic sites	1 vs >1	1.24	.57
MSKCC risk group	Favorable vs intermediate vs poor	1.13	.70[a]
Treatment	Sorafenib vs sunitinib	0.77	.39
TSH_{max2}, μM/mL	≤3.77 vs >3.77	0.91	.79

PFS indicates progression-free survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; MSKCC, Memorial Sloan-Kettering Cancer Center; TSH_0, baseline serum thyroid-stimulating hormone (TSH) level; VEGF, vascular endothelial growth factor; HR, hazard ratio; TSH_{max1}, highest serum TSH level measured within 1 month after treatment initiation; TSH_{max2}, highest serum TSH level measured within 2 months after treatment initiation.

[a] Trend test.

[b] The first variable category listed is the reference category.

Table 6. Univariate and Multivariate Analyses of Overall Survival

		Univariate Analysis: OS	
Variable	No. of Patients	Median Survival (95%CI), mo	Log-Rank *P*
Time from diagnosis to treatment			**.70**
≤1 y	45	NR (13.4-NR)	
>1 y	42	25.4 (12.5-NR)	
ECOG PS			**.15**
0	72	NR (13.9-NR)	
≥1	15	17.5 (6.7-25.4)	
No. of metastatic sites			**.30**
1	26	NR (13.4-NR)	
>1	61	25.4 (12.2-NR)	
Metastatic site lung			**.29**
Yes	60	18.3 (13.7-NR)	
No	27	NR (12.5-NR)	
Metastatic site liver			**.24**
Yes	15	13.9 (10.5-NR)	
No	72	NR (14.1-NR)	
Metastatic site bone			**.34**
Yes	33	14.1 (10.7-NR)	
No	54	NR (13.9-NR)	
Metastatic site CNS			**.49**
Yes	6	17.5 (12.2-NR)	
No	81	25.4 (13.9-NR)	
MSKCC risk group			**.14[a]**
Favorable	20	NR (14.1-NR)	
Intermediate	62	25.4 (13.4-NR)	
Poor	5	10.5 (4.6-NR)	
TSH_0, μM/mL			**.057**
>3.77	5	NR (NR-NR)	
≤3.77	73	17.5 (13.4-NR)	
Prior treatment cytokines			**.41**
Yes	55	18.3 (12.5-NR)	
No	32	NR (14.1-NR)	
Prior treatment anti-VEGF			**.24**
Yes	25	13.9 (8.4-NR)	
No	62	NR (14.1-NR)	

		Multivariate Analyses: OS	
Variable	Variable Category[b]	HR	*P*
OS and TSH_{max1}, n = 82 evaluable patients			
Time from diagnosis to treatment, y	≤1 y vs >1 y	0.95	.89
ECOG PS	0 vs ≥1	1.36	.52
No. of metastatic sites	1 vs >1	1.04	.94
MSKCC risk group	Favorable vs intermediate vs poor	1.54	.30[a]
Treatment	Sorafenib vs sunitinib	0.67	.33
TSH_{max1}, μM/mL	≤3.77 vs >3.77	0.37	.07
OS and TSH_{max2}, n = 83 evaluable patients			
Time from diagnosis to treatment	≤1 y vs >1 y	1.15	.72
ECOG PS	0 vs ≥1	1.41	.44
No. of metastatic sites	1 vs >1	1.14	.77
MSKCC risk group	Favorable vs intermediate vs poor	1.99	.11[a]
Treatment	Sorafenib vs sunitinib	0.65	.27
TSH_{max2}, μM/mL	≤3.77 vs >3.77	0.31	.014

OS indicates overall survival; CI, confidence interval; NR, not reached; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; MSKCC, Memorial Sloan-Kettering Cancer Center; TSH_0, baseline serum thyroid-stimulating hormone (TSH) level; VEGF, vascular endothelial growth factor; HR, hazard ratio; TSH_{max1}, highest serum TSH level measured within 1 month after treatment initiation; TSH_{max2}, highest serum TSH level measured within 2 months after treatment initiation.

[a] Trend test.

[b] The first variable category listed is the reference category.

on univariate or multivariate analysis. In contrast, when we tested these factors for their impact on OS, TSH_{max1} and TSH_{max2} $\leq$3.77 μM/mL were associated with worse survival on univariate analysis ($P = .044$ and $P = .016$, respectively). On multivariate analysis, only a TSH_{max2} increase >3.77 μM/mL was an independent predictor of survival ($P = .014$; HR, 0.31).

DISCUSSION

To the best of our knowledge, this is the first prospective analysis to demonstrate that hypothyroidism, which is a frequent side effect from treatment with sorafenib and sunitinib, predicts the course of the disease in patients with mRCC. We observed that patients who had subclinical hypothyroidism during treatment with sunitinib or sorafenib had a significantly greater probability of responding to treatment. Moreover, an increase in TSH within 2 months of starting treatment was associated with significantly longer survival compared with the survival of patients without hypothyroidism. Finally, the development of hypothyroidism within 2 months of treatment was an independent predictor of survival. Our data are supported by the preliminary findings of Wolter, who reported that patients with thyroid function abnormalities who received sunitinib had a longer PFS than patients without such abnormalities.[31] In contrast to hypothyroidism, the classic MSKCC[30] prognostic criteria did not reach statistical significance in our population, which may have been related to the smaller number of patients in our trial compared with larger study populations.

In clinical oncology, correlations between hypothyroidism and outcomes occasionally have been observed.[19-25,27] It has been suggested that the thyroid hormone itself, by stimulating other growth factors, may represent a growth-stimulating signal in various tumor types.[32] Thus, a hypothyroid state appears to constitute an advantage for cancer patients. In this context, it is interesting to note that, in our current study, the few patients who had baseline hypothyroidism had a longer survival than the patients without baseline hypothyroidism. Because hypothyroidism is uncommon in the general population,[33] it is possible that patients with cancer may benefit from drugs that induce changes in thyroid function.

It is unclear whether the induction of hypothyroidism is part of the mode of action of sunitinib and sorafenib or whether it merely represents a pharmacokinetic epiphenomenon that results from a more appropriate individual dose. Hypothyroidism per se may lead to the modulation of paracrine growth factors, such as epidermal growth factor,[34] insulin-like growth factor-I,[35] and others.[36] Berg et al[36] have reported that the membrane protein integrin ($\alpha v\beta_3$) contains a cell surface receptor site for thyroid hormone that is linked to the activation of mitogen-activated protein kinase (MAPK) and angiogenesis. In addition, others have demonstrated that neoangiogenesis may be decreased by hypothyroidism. The occurrence of hypothyroidism also may reflect differences in pharmacokinetics, affinity to receptor tyrosine kinases, and individual dose. TKIs are prescribed independently from the weight and height of patients and have demonstrated high interpatient pharmacokinetic variability.[37] In our study, the median PFS of euthyroid patients who received sorafenib patients was consistent with previous reports (5.5 months),[5] whereas hypothyroid patients who received sorafenib achieved a median PFS of 19 months. This may reflect a better individual pharmacokinetic profile. Therefore, we believe that both drug-induced hypothyroidism per se and interpatient pharmacokinetic variability may explain our results.

Receptor-TKIs represent a considerable improvement for the majority of patients with RCC; however, not all patients respond to treatment, and some may benefit more from other novel therapeutic strategies. To optimize and individualize treatment in mRCC, predictive factors are urgently required. To date, in the case of novel agents, only a few predictive factors have been reported: It has been proposed that the expression patterns of hypoxia-inducible factor alpha 1 and 2—intracellular proteins that are up-regulated differentially in RCC—may facilitate the selection of targeted therapy.[38] However, such analyses might not be feasible in routine clinical practice. In contrast, the ability of a drug to rapidly induce hypothyroidism might serve as a broadly available surrogate biomarker. The practicability of clinical biomarkers also has been described by Rini et al, who reported that the induction of a diastolic blood pressure increase predicted survival in patients who received treatment with axitinib.[39] Moreover, a biomarker could serve as an additional criterion for assessment of response to these TKIs. RECIST criteria are not appropriate for assessing response in the case of targeted agents, because cavitation and necrosis often are observed before a decrease in tumor volume can be detected.[40] Thus, together with radiologic findings, the occurrence of hypothyroidism may facilitate the decision to continue treatment by reflecting more accurately the true therapeutic benefit.

Our findings raise 4 major questions: First, the swiftness with which hypothyroidism develops needs to be clarified. In our analysis, the time of TSH assessment was chosen arbitrarily and represented a snap-shot of the thyroid function during treatment. In our series, all hypothyroid patients were diagnosed with increased TSH within the first 8 weeks of treatment. Those who had no increase within 2 months remained euthyroid for the entire treatment period. However, some patients may present with hypothyroidism later, and these patients may benefit like the patients who have hypothyroidism diagnosed earlier. In contrast, TSH also may be increased already within the first 1 or 2 weeks, thereby allowing for an early change in treatment. Second, it remains unclear whether the degree of TSH increase is relevant for treatment outcome. We did not observe a correlation between TSH levels and outcomes; however, this might be related to the relatively small number of patients in the current analysis. Third, the role of thyroid hormone-replacement therapy remains to be determined. If induction of hypothyroidism is part of the mode of action of sunitinib and sorafenib, then levothyroxine may undermine the antitumor efficacy of these agents. In our cohort, levothyroxine treatment did not have an impact on outcome, but most of our patients remained in a hypothyroid state despite replacement therapy. Fourth, it is unclear whether an increased TKI dose might lead to hypothyroidism (and, possibly, to an associated response) in patients who do not present a priori with hypothyroidism at the standard dose.

In conclusion, the current results indicated that sunitinib and sorafenib induced hypothyroidism in a large number of patients. Hypothyroidism no longer should be perceived as an unwanted side effect of treatment but, rather, as predictive marker for treatment outcome in patients with mRCC. To define the full potential of this biomarker compared with other prognostic and predictive factors, future studies should include a larger number of patients. Moreover, the role of this phenomenon should be investigated in other types of cancer.

CONFLICT OF INTEREST DISCLOSURES

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