Vanishing thyroid in patients with renal cell carcinoma treated with tyrosine kinase inhibitor

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Purpose

Although most patients with early-stage renal cell carcinoma (RCC) can be cured surgically, approximately 33% of patients present with metastatic disease for which the treatment usually is not curative [1]. In addition, approximately 50% of patients who undergo potentially curative surgery for less advanced disease can be expected to develop a recurrence with distant metastases [2]. Recently, tyrosine kinase inhibitors against the vascular endothelial growth factor (VEGF) pathway have become an attractive care for patients with metastatic RCC [3,4]. Sunitinib is an oral tyrosine kinase inhibitor with potent activity against several related protein tyrosine kinase inhibitors, including VEGF receptors 1 to 3, platelet-derived growth factor (PDGF) receptor-#, stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3. Sorafenib is also an oral multikinase inhibitor that, in addition to inhibiting VEGF receptors 1 to 3, also inhibits the serine threonine kinase Raf-1 involved in the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)/extracellular signal-regulated kinase signaling pathway activated after VEGF binding. Both sunitinib and sorafenib have been shown to be safe and effective for the treatment of metastatic RCC in vivo as well as in vitro with direct anti-tumor effects and anti-angiogenetic effects [5-8] and has been standard treatment to metastatic RCC in NCCN guidelines™ [9].

Fatigue due to hypothyroidism is a frequent toxic effect of these novel molecularly targeted drugs, especially sunitinib, and several investigators have demonstrated that regular surveillance of thyroid function including serum thyroid-stimulating hormone (TSH) measurement is warranted in patients receiving sunitinib and replacement therapy should be undertaken as clinically indicated [10-14]. However, to the best of our knowledge, there have been no reports of pursuing the thyroid size using radiological imaging modalities in RCC patients treated by sunitinib and sorafenib. Therefore, if we are able to predict the depression of thyroid function on follow-up CT images, it will be clinically interesting. The purpose of this study is to evaluate the relationship between the thyroid size shown on CT and thyroid function in patients with metastatic RCC treated with sunitinib and sorafenib.
Methods and Materials

Subjects

Thirty-two patients (25 male and 7 female, 67.8±9.3 years) with metastatic renal cell carcinoma had began the treatment by sorafenib (n=22) and sunitinib (n=10) from April 21, 2008 and June 5, 2009 after approval from the institutional review board. An informed consent was obtained from each patient after the nature of the procedure had been fully explained. CT scans were performed before, and 3, 6, 9, and 12 months after the initiation of the treatment for the purpose of checking treatment response. Thyroid function test including free T3, free T4, and TSH was performed before and every one or two weeks after the beginning of the treatment. The patients who ever showed elevated Thyroid-stimulating hormone (TSH) >10 mU/l were defined as "hypothyroidism".

Image analysis and data interpretation

All patients underwent body CT from neck to pelvis by 64-MDCT scanner (Aquilion 64; Toshiba Medical System, Nasu, Japan) with following parameters: 64×0.5 mm detector collimation, 0.5 sec/gantry rotation, 120 kVp, 350 mA, 32-35 cm field-of-view (FOV) and 0.94 beam pitch. Using reconstructed axial images of 5 mm thickness, on a section of CT images showing the maximum area, a region of interest was placed over the bilateral thyroid, and the area (mm²) was calculated by an experienced radiologist. The area of the thyroid was assessed twice in the same image, and the average was calculated.

Statistical analysis

Differences in thyroid size were compared between the patients groups with or without "hypothyroidism" over time, as well as the type of the drug, using repeated-measures ANOVA. Differences in thyroid size between two groups at the separate time points were assessed with unpaired t-test. Receiver operating characteristic (ROC) curve was drawn to determinate the optimal cutoff values of percentage from pre-treatment that would best guess patients group with "hypothyroidism". All statistical analyses were performed using SPSS software (version 13.0, SPSS Inc.) for windows and p values less than 0.05 were considered to be statistically significant.
Results

Eight of 22 patients (36%) treated with sorafenib presented "hypothyroidism", and eight of 10 patients (80%) treated with sunitinib presented "hypothyroidism". These 16 patients (8 sorafenib, 8 sunitinib) presented "hypothyroidism" 97.1±91.0 days (range: 12-315 days) after the beginning of the treatment.

Thyroid sizes of patients with "hypothyroidism" were 603±253 mm$^2$ before the treatment, 521±248 mm$^2$ after 3 months, 464±235 mm$^2$ after 6 months, 396±189 mm$^2$ after 9 months, and 386±157 mm$^2$ after 12 months, whereas those of patients without "hypothyroidism" were 658±210 mm$^2$, 620±189 mm$^2$, 595±222 mm$^2$, 609±199 mm$^2$, and 594±181 mm$^2$, respectively (Fig. 1). In patients with "hypothyroidism", the thyroid reduced in size of 87±18% after 3 months, 78±22% after 6 months, 67±22% after 9 months and 64±23% after 12 months, whereas in the patients without "hypothyroidism", the thyroid reduced in size of 96±11%, 90±13%, 93±14% and 91±13%, respectively. The pattern of the change in thyroid size over time was significantly different between patients with and without "hypothyroidism" (p=0.0027, repeated-measures ANOVA). Differences (p-value) in thyroid size between two groups at 3, 6, 9, and 12 months follow-up were 0.13 0.087, 0.00054, and 0.00043, respectively.

Using a percentage change from pre-treatment baseline in thyroid size cutoff of -9.3%, the sensitivity and specificity to guess patients group with "hypothyroidism" at 3 months follow-up period were 62.5% and 62.5% respectively. Using a percentage change from pre-treatment baseline in thyroid size of -11.9%, the sensitivity, specificity, and accuracy to guess patients group with "hypothyroidism" at 6 months follow-up period were 68.8%, and 56.3%, respectively. Using a percentage change from pre-treatment baseline in thyroid size of -16.6%, the sensitivity, specificity, and accuracy to guess patients group with "hypothyroidism" at 9 months follow-up period were 75.0% and 68.8%, respectively. Using a percentage change from pre-treatment baseline in thyroid size of -19.2%, the sensitivity, specificity, and accuracy to guess patients group with "hypothyroidism" at 12 months follow-up period were 81.3% and 75.0%, respectively.

We also evaluated the differences in thyroid size between 8 patients treated with sorafenib and 8 patients with sunitinib showing "hypothyroidism" over time. Thyroid sizes of 8 patients receiving sorafenib were 498±133 mm$^2$ before the treatment, 447±165 mm$^2$ after 3 months, 444±174 mm$^2$ after 6 months, 402±127 mm$^2$ after 9 months, and 380±897 mm$^2$ after 12 months, whereas those of 8 patients receiving sunitinib were 709±307 mm$^2$, 595±303 mm$^2$, 484±296 mm$^2$, 389±246 mm$^2$, and 391±211 mm$^2$, respectively (Fig. 2). In 8 patients treated with sorafenib, the thyroid reduced in size of 88±13% after 3 months, 88±18% after 6 months, 81±13% after 9 months and 78±13% after 12 months, whereas in 8 patients with sunitinib, the thyroid reduced in size of 86±23%, 68±23%, 54±22%
and 50±22%, respectively. The pattern of the change in thyroid size over time was not significantly different between patients with and without "hypothyroidism" (p=0.039, repeated-measures ANOVA). Differences (p-value) in thyroid size between two groups at 3, 6, 9, and 12 months follow-up were 0.82, 0.078, 0.013, and 0.0089, respectively.

Thyroid replacement therapy was undertaken in 2 of 8 patients (25%) treated with sorafenib in group A and 7 of 8 patients (87.5%) treated with sunitinib in group A.

A representative case showing "hypothyroidism" was shown in Fig. 3.
Conclusion

After tyrosine kinase inhibitor treatment, the thyroid showed apparent size reduction in the patients with hypothyroidism, especially treated with sunitinib. Measurement of thyroid size on CT may provide useful additional information in RCC patients treated with tyrosine kinase inhibitor treatment.
References


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