Morphological and functional alterations of thyroid gland during treatment with tyrosine kinase inhibitors in advanced renal cell carcinoma

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Introduction
Sunitinib (SUN) is a novel oral multitarget tyrosine-kinase inhibitor (TKI) that has demonstrated its efficacy in the treatment of metastatic renal cell carcinoma (mRCC). The thyroid dysfunction is one of the most common side effects of SUN. The mechanisms inducing thyroid dysfunction are still poorly understood.

Objectives
Identify the incidence, severity, ultrasonographic changes and pattern of response of thyroid function tests during treatment with SUN.

Methods
This ongoing prospective observational study to date has completed the evaluation of 25 mRCC patients: 10 women (59±18 yrs) and 15 men (65.5±7 yrs). 5/25 patients received LTF4 replacement therapy and 11/25 had thyroid nodules at enrollment.

SUN was administered at daily dose of 50 mg (schedule 4/2). Thyroid function tests were assessed at baseline and at week-4 and -6 of each cycle, ultrasound at baseline and after the first and the third cycle (See design of the study).

Results
We observed an increase in TSH values, most frequently after the second cycle of SUN (mean-TSH 17.05±4.35 μIU/mL) and in older men (mean-TSH 91.95±106.4 μIU/mL). TSH rose above normal range (0.35-4.94 μIU/mL) only in patients which were not on LTF4 replacement at enrollment.

Half of untreated patients had an increase of TSH which required L-T4 substitution after the first cycle; all of them required a further dosage increase after the second cycle. Patients already on L-T4 at the enrollment required no dose-adjustment at any cycle. No significant changes occurred in thyroid immunity.

Conclusions
SUN is associated with thyroid functional and morphological changes occurring rapidly, within few weeks, in most but not all patients. Distinct individual patterns of response to TKI are identified allowing a better prognosis and management. The development of thyroid nodules and the mechanisms by which SUN impairment thyroid function deserve further investigations.

References
- Sunitinib-induced hypothyroidism is associated with increased type 3 diolotion. Abirman RM. et al. J. Clin Endocrinol Metab 2010

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