Topic: **HYPOTHYROIDISM AFTER TREATMENT OF GASTRO-INTESTINAL CANCER**

Title: Hypothyroidism after 'Sunitinib' treatment for patients with gastrointestinal stromal tumors.

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SUMMARY

Background: Sunitinib malate is an oral tyrosine kinase inhibitor recently approved for the treatment of gastrointestinal stromal tumors and renal carcinoma. Because the ret proto-oncogene is also inhibited by this agent, clinical evaluation of thyroid function was performed.

Objective: To describe the prevalence and clinical presentation of thyroid dysfunction related to Sunitinib therapy.

Design: Prospective, observational cohort study.

Setting: Tertiary care hospital.

Patients: 42 patients treated for a median of 37 weeks (range: 10-167 weeks).

Measurements: Following analysis of serial TSH measurements collected prospectively during a clinical trial of sunitinib, the proportion of patients with thyroid dysfunction was determined.

Results: Abnormal serum TSH concentrations were documented in 26 of 42 patients (62%); 15 (36%) developed persistent, primary hypothyroidism; 4 (10%) developed isolated TSH suppression; and 7 (17%) experienced transient, mild TSH elevations. The risk for hypothyroidism increased with the duration of sunitinib therapy. Six of 15 (40%) hypothyroid patients had suppressed TSH concentrations before developing hypothyroidism, suggesting thyroiditis. Two hypothyroid patients evaluated with thyroid ultrasonography had no visualized thyroid tissue despite normal baseline thyroid function.

Limitations: The exploratory nature of this study precluded more frequent biochemical and ultrasonographic analysis that may better define the mechanisms of sunitinib-associated thyroid dysfunction.

Conclusion: Hypothyroidism is a frequent complication of sunitinib therapy. Regular surveillance of thyroid function is warranted in patients receiving this drug. Although the mechanism by which this complication occurs is unknown, the observations of preceding TSH suppression and subsequent absence of visualized thyroid tissue in some patients suggest that sunitinib may induce a destructive thyroiditis through follicular cell apoptosis. This provides a rationale for further investigation of sunitinib treatment in patients with advanced thyroid cancer.

COMMENT

Tyrosine kinase inhibitors are molecules belonging to new lines of treatment in oncology and have been shown to be beneficial for the treatment of numerous malignant conditions. These molecules have been pharmaco-modeled to block the activity of selected kinase signalling enzymes, but it is increasingly evident that their effects may overlap the 'theoretical' selectivity and, in turn, have undesirable effects on several kinase pathways. Sunitinib (SUTENT®) has recently been approved in USA and Europe for the treatment of patients with metastatic or surgically unresectable disease. After the identification of 2 index cases who developed primary hypothyroidism, the authors of the present study expanded their original observations to a large group of patients treated with Sunitinib.

They show herein that 36% of the patients developed hypothyroidism after an average of 50 weeks of therapy. Patients in this study had a normal thyroid function before therapy and the data suggest that this kinase inhibitor induced some sort of destructive thyroiditis by a yet unknown mechanism associated with the drug. The article does not give details about a possible thyroid function recovery after stopping the drug, but it mentions TSH normalization after combined l-thyroxine administration.

Primary hypothyroidism is a rare complication of therapeutic drugs, but has been described with several agents, such as Lithium, interferon-alpha and interleukins, amiodarone and other iodine-containing agents, phenytoin, carbamazepine, rifampicine, etc.

Finally, the implication of the present study is the need to monitor thyroid function regularly in patients treated with this (and other) tyrosine kinase inhibitors and obviously also treat those patients who develop hypothyroidism with l-thyroxine.

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See Table below

Table. **Serum Thyroid-Stimulating Hormone Concentrations in 15 Patients Who Developed Hypothyroidism during Sunitinib Therapy for the Treatment of Gastrointestinal Stromal Tumors**

Patient	Age, *y*	Duration of Sunitinib Therapy, *wk*	Time to Persistent Elevation of TSH Levels, *wk*	TSH Concentrations during Sunitinib Therapy, *mU/L*		Evidence of Thyroiditis†
				Baseline	Maximum	
1	37	98	55	1.6	288	No
2	36	151	53	3.9	247	Yes
3	26	79	71	4.6	99	No
4	57	102	84	0.9	94	Yes
5	68	105	38	0.7	56	No
6	77	94	29	2.4	32	No
7	69	167	94	1.5	31	No
8	37	162	28	2.4	30	Yes
9	44	99	64	0.4	24	Yes
10	68	17	12	2.8	12	No
11	45	129	12	3.7	11	No
12	73	86	86	2.2	11	No
13	47	95	53	1.8	9.0	No
14	58	132	41	1.3	7.6	Yes
15	44	37	31	1.4	7.2	Yes

* TSH = thyroid-stimulating hormone.
† TSH concentration less than 0.5 mU/L before elevation of TSH levels and initiation of L-thyroxine therapy.