

SUNITINIB CAUSES HYPOTHYROIDISM BY REGRESSION OF THYROID CAPILLARIES AND ENHANCEMENT OF TYPE 3 DEIODINASE ACTIVITY

Kappers MH, van Esch JH, Smedts FM, de Krijger RR, Eechoute K, Mathijssen RH, Sleijfer S, Leijten F, Danser AH, van den Meiracker AH, Visser TJ. **Sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression.** J Clin Endocrinol Metab. August 3, 2011 [Epub ahead of print].

SUMMARY ●●●●●●●●●●●●●●●●

BACKGROUND

The tyrosine kinase inhibitor, sunitinib (Sutent), approved for treatment of metastatic renal-cell cancer and gastrointestinal stromal tumor, causes hypothyroidism in a high proportion of patients taking it. The drug inhibits multiple kinases, including the vascular endothelial receptors. The mechanism responsible for the hypothyroidism is still unclear. This study aimed to investigate further the incidence, time course, and mechanism of the hypothyroidism.

METHODS

The study consisted of three components: a retrospective clinical study of 83 patients who had thyroid tests based on clinical indications during sunitinib therapy; a prospective study of 15 patients who had thyroid tests before treatment and at the end of the first and second 4-week treatment cycles; a study of rats treated with sunitinib at a dose of 26.7 mg per kilogram per day for 8 days, and suitable controls. At the end of the treatment period, serum thyroid-function tests were measured, thyroid histology was assessed, and deiodinase type 1 (D1) and type 3 (D3) activities were measured in liver tissue.

RESULTS

In the retrospective study, 35 patients (42%) had

an elevated serum thyrotropin (TSH) with a mean time to onset of 90 days (range, 14 to 856); the maximum TSH was observed at a mean of 221 days (range, 20 to 1033). A total of 5 of the 35 had a suppressed serum TSH preceding the elevated serum TSH by 117 to 235 days. In the prospective study, the mean serum TSH doubled after the second cycle of therapy. Although serum free thyroxine (T_4), triiodothyronine (T_3), and reverse T_3 were not significantly changed, the ratio of T_3 to reverse T_3 was slightly reduced. Antithyroid peroxidase antibody levels were not affected.

In the rats, serum T_4 and T_3 were slightly reduced by sunitinib, as compared with controls. Sunitinib treatment reduced hepatic D1 and increased hepatic D3 activity, and these changes were reversible after stopping sunitinib. Thyroid histology showed a decrease in the number of capillaries with sunitinib treatment, but no change in larger vessels. When the treatment was stopped, there was a rebound increase of capillary numbers. Treatment with an endothelin receptor antagonist partially prevented the sunitinib-induced reduction of capillaries.

CONCLUSIONS

Sunitinib induces hypothyroidism due to changes in T_4 and T_3 metabolism as well as causing thyroid capillary regression.

COMMENTARY ●●●●●●●●●●●●●●●●

This is an excellent study of the mechanism responsible for sunitinib-induced hypothyroidism. The retrospective study confirms similar retrospective studies concerning the incidence of hypothyroidism in patients treated with this drug (1, 2). In other studies (3, 4), it has been proposed that destructive

thyroiditis is responsible for the hypothyroidism, but the small proportion of patients with suppressed TSH in this study and the very long lag time for development of hypothyroidism make antecedent thyroiditis an unlikely explanation for the hypothyroidism experienced by most patients. In the prospective study, the small change in the ratio of T_3 to reverse T_3 suggests a

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reduction of D1 and increase of D3. Sunitinib therapy is associated with nausea, reduced food intake, and weight loss, raising the issue of changes in thyroid tests similar to those in nonthyroid illness. The studies in rats were more convincing with regard to changes in deiodinase activities. However, the rats were treated with a very high dose of sunitinib and did not gain as much weight as the controls. Although it is possible that the results were slightly affected by altered nutrition, the changes in deiodinase activity were reversible when the drug was stopped for only 11 days. The authors hypothesize that sunitinib may increase hypoxia-induced factor 1 that in turn increases D3 activity, as they reported previously (5), and that this process could be triggered by hypoxia caused by reduction of capillary blood flow.

In patients with hypothyroidism who are taking sunitinib and similar tyrosine kinase inhibitors, there is frequently an increase in the requirement for thyroxine to maintain the target TSH, and this has not been adequately explained. It is possible that the reduction of D1, a pathway producing the active thyroid hormone, and increase of D3, a pathway of T₄ disposal, provide some explanation for the increased thyroxine requirement. I expect that this very productive group in Rotterdam are engaged in studies of this hypothesis, even though they did not comment on it in this paper.

— Jerome M. Hershman, MD

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