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Role of sunitinib–induced hypothyroidism in oncological patients

Abstract

Sunitinb (SUN) belongs to a new class of multi targeted tyrosine kinase inhibitors (TKIs) used in treatment of metastatic renal cell carcinoma, gastrointestinal stromal tumors and pancreatic neuroendocrine tumors. Although generally well tolerated with favourable safety profile, SUN has distinct side effects that differ from the standard chemotherapy and require monitoring and management. Hypothyroidism is one of the most important adverse events induced by SUN. It is usually subclinical and rarely severe, with variable incidence. The potential mechanisms involved in thyroid dysfunction are not fully understood. Generally, SUN–induced hypothyroidism does not require discontinuation of cancer therapy but only needs the thyroid replacement therapy. The occurrence of SUN–induced hypothyroidism appears with successful treatment in term of survival of oncological patients but more clinical investigations are necessary to validate this correlation.

Keywords: sunitinb, receptor, chemotherapy agents, thyroid function

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Abbreviations: SUN, sunitinb; TKIs, tyrosine kinase inhibitors; CTC, common toxicity criteria; TPO, thyroid peroxidase.

Introduction

The tyrosine kinase inhibitors (TKIs) are enzymatic receptor proteins designed to block the ATP–binding site in tyrosine kinases involved in several cellular processes such as, proliferation, differentiation, survival, migration and angiogenesis. Although their mechanism of action is the same, they differ in the spectrum of targeted kinases, pharmacokinetics and specific adverse events.[1] TKIs have different toxicity than conventional chemotherapy agents.[2] The side effects are rarely life–threatening but may reduce quality of life.[3] Many of the most common adverse effects occur during the treatment with all the TKIs, while others are more specific to individual agents.[4] "This mini–review aims to examine the effects of SUN treatment on thyroid function and the role of SUN–induced hypothyroidism as a possible predictive factor for the outcome of the cancer treatment."

Sunitinib

Sunitinib (SUN) is an oral, small–molecule TKI that is structurally similar to adenosine triphosphate. It has been approved by the Food and Drug Administration for patients with metastatic renal cell cancer (mRCC), imatinib–resistant gastrointestinal stromal tumor and advanced pancreatic neuroendocrine tumor.[5–7] SUN inhibits cellular signaling by targeting multiple receptor tyrosine kinases, including all receptors for the three isoforms of VEGF, PDGF, FMS–like tyrosine kinase–3 and stem cell factor receptor. SUN also binds RET, CD114 and CD135 receptors.[8–13] The simultaneous inhibition of these targets reduces tumor vascularization and triggers cancer cell apoptosis, thus resulting in tumor shrinkage. The recommended dose of SUN is 50mg oral dose taken once daily, on a schedule of 4weeks on treatment followed by 2weeks off. Dose interruption and/or dose modification in 12.5mg increments or decrements is recommended based on individual safety and tolerability. The daily dose should not exceed 75mg and not drop below 25mg.

SUN is generally well tolerated and the frequency of common toxicity criteria (CTC) grade 3 or 4 is low (≤10%). However, some distinct side effects require monitoring and treatment. The most common adverse events associated with SUN therapy are fatigue, diarrhoea, nausea, anorexia, hypertension, a yellow skin discoloration, hand–foot skin reaction, hypothyroidism, stomatitis, altered taste and constipation.[2,14,15] The side effects can be managed through supportive care, dose interruption or reduction.

Sunitinib and thyroid dysfunction

Biochemical and clinical hypothyroidism is commonly reported in SUN treated patients.[16–18] Its prevalence in the various studies varies from 50–85% in retrospective trials.[16,19] to 36–46% in prospective and observational studies.[20–27] This discrepancy is probably due to differences in the study design, sample size, definition of hypothyroidism and previous use of cytokine therapy.[22]

Hypothyroidism induced by SUN is usually subclinical (TSH elevation alone with normal FT4 levels) or overt (TSH elevation and low FT4) but rarely severe.[21] In general, thyroid dysfunction arises from 12 to 50weeks after starting SUN and is correlated with treatment duration.[28] The mechanism of SUN–associated hypothyroidism is unclear and the course of the disease is not fully understood.[22,24] Several underlying mechanisms might be involved: reduced synthesis of thyroid hormones through inhibition of thyroid peroxidase (TPO) activity and progressive depletion of the thyroid reserve;[19] inhibition of iodine thyroidal uptake;[21] glandular atrophy induced by TKIs through the inhibition of vascularisation (direct action on VEGFR and/or PDGFR);[29,30] possible autoimmune damage that causes lymphocytic thyroiditis in patients receiving SUN.[22,31] As regards thyroid ultrasound assessment, the majority of literature demonstrated a progressive reduction in thyroid size, mainly after three months of SUN treatment, regardless of the SUN phase (ON/OFF). This was combined with marked hypoechogenicity and reduced parenchymal perfusion, probably as a result of SUN's anti–angiogenic effect.[32–34]

Hypothyroidism and cancer's outcome

SUN–induced hypothyroidism has also been proposed as a possible predictive factor for the outcome of the cancer treatment, although the conclusions are still unclear.[23–27,35,36] A preliminary study of SUN treatment for mRCC suggested that hypothyroid patients had a significantly longer PFS than euthyroid patients.[22] Schmidinger prospectively studied the correlation between the onset of hypothyroidism and the rate of disease remission, discovering a higher overall response rate in hypothyroid than in euthyroid patients (ORR: 28.3% vs. 3.3%; p<0.001).[24] Recently, Buda–Nowak showed that patients who had developed hypothyroidism had better median progression free survival to patients with normal thyroid function 28,3months.95% (CI) 20.[4–36] 2months *versus* 9.8months (6.4–13.1months), recommending, during SUN treatment, the thyroid evaluation regularly.[37] In contrast, in a prospective observational multicentre study, Sabatier found that thyroid dysfunction did not increase survival in SUN–treated patients with mRCC; after six months of SUN, 53% of patients developed hypothyroidism, with a median PFS of 18.9months compared to 15.9 for the euthyroid group.[27] More clinical investigations are necessary to explain the correlation between thyroid function and progression free survival/ overall survival and the possible clinical usefulness of TSH as potential tumor biomarker in SUN–treated patients.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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