Sorafenib-induced Thyroiditis in FMS-like Tyrosine Kinase 3-internal Tandem Duplication-mutated Acute Myeloid Leukemia

Jie Sun, Juan Hu, Yan Huang, Shuang-Wei Ying, Xiao-Yan Han, Yan-Long Zheng, He Huang
Bone Marrow Transplantation Centre, The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang 310003, China

To the Editor: Sorafenib is a novel, orally available inhibitor of multiple kinases. It has been used in relapsed and refractory FMS-like tyrosine kinase (FLT)-3-positive acute myeloid leukemia (AML) in recent years with favorable outcomes. Thyroiditis and hypothyroidism as side effects have been reported in treatment on renal cell cancer. Here, we report a case of FLT3-internal tandem duplication (ITD)-positive AML, who developed subacute thyroiditis during treatment with sorafenib. Thyroiditis was controlled with sorafenib withdrawal and the use of dexamethasone. No thyroid dysfunction was detected under follow-up. Our experience shows that close monitoring of thyroid function is necessary in AML patients under sorafenib treatment.

A 35-year-old female was diagnosed with FLT3-ITD-positive AML (AML-5b). Routine blood examinations revealed white blood cell (WBC) count 104.9 x 10^9/L, hemoglobin 46 g/L, platelet count 180 x 10^9/L, and blast cells 50%. She was a hepatitis B virus (HBV) carrier with HBV-DNA copies less than the minimum detection level (reference range: 0–1000 U/ml). Lamivudine was administered.

She received induction chemotherapy as intra-arterial (idarubicin 8 mg/m² on days 1–3 and cytarabine 100 mg/m² on days 1–5). On day 7 after induction chemotherapy, the bone marrow smear was rechecked. Bone marrow pro plus pre-monocytes were 5% and minimal residual disease (MRD) was 0.27%. However, at 27 days after chemotherapy, a bone marrow examination showed that pro plus pre-monocytes were 66%. She received the second cycle of chemotherapy with a dose-reduced AAE (aclarubicin 20 mg, days 1–3; cytarabine 100 mg/m², days 1–5; and etoposide 100 mg, days 1–3) plus sorafenib (400 mg bid, orally). The chemotherapy dose was reduced because the patient developed gastric hemorrhage. One month later, a routine bone marrow examination showed low myeloproliferation, 10% pro plus pre-monocyte cells, and 1.79% MRD. The WBC count was <2.5 x 10^9/L, and platelet count was 20 x 10^9/L.

On day 37 of sorafenib therapy, the patient felt a neck mass with pain and fever. She felt pain in the region of the thyroid, especially during swallowing with a pain scale score at 5; the neck mass enlarged quickly during the 1st week; and her temperature was as high as 39°C. She stopped taking sorafenib by herself 2 days after neck pain was happened. No weight loss, irritability, anxiety, insomnia, or fatigue was found. Physical examination showed thyroid swelling, with diffuse tenderness and warmth but no redness. Routine blood examinations revealed WBC count, 2.5 x 10^9/L; neutrophil, 45%; hemoglobin, 43 g/L; and platelet count, 33 x 10^9/L. C-reactive protein (CRP) was 228.3 mg/L and a thyroid function test was normal. An antinuclear antibody test was negative; blood culture was negative; tests for Epstein–Barr virus, cytomegalovirus, and hepatitis A, C, D, E, F, and G were all negative; hepatitis B was positive, but (HBV)-DNA copies was below the detection limit. Neck computed tomography (CT) with intravenous (iv) contrast showed thickening of both sides of the pharynx oralis and enlargement of both sides of the thyroid gland with unequal density. Thyroid ultrasonography showed an increasing size of the thyroid gland on the inferior side and edema of the surrounding soft tissue. Emission CT for thyroid showed that technetium uptake was 0.67% (normal range: 0.24%–3.34%). Subacute thyroiditis was diagnosed.

She was given dexamethasone 5 mg iv, daily, days 1–4, then prednisone 30 mg, daily, for 2 weeks, and then tapered to discontinuation for 1 month. After dexamethasone was used, the symptoms of pain and swelling alleviated quickly. Serum CRP dropped to 36.3 mg/L 1 week after therapy. The patient left hospital with no pain and a normal-sized thyroid 1 week after admission. During follow-up in the next 3 months, her thyroid function remained normal.

Unfortunately, the patient developed sorafenib-resistance after 3 months of administration. Hematologic relapse was diagnosed, and she died of relapse 6 months after the primary diagnosis.

Address for correspondence: Prof. He Huang,
Bone Marrow Transplantation Centre, The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang 310003, China
E-Mail: hehuang.zju@gmail.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

© 2016 Chinese Medical Journal; Produced by Wolters Kluwer - Medknow

Received: 22-06-2016 Edited by: Ning-Ning Wang
How to cite this article: Sun J, Hu J, Huang Y, Ying SW, Han XY, Zheng YL, Huang H. Sorafenib-induced Thyroiditis in FMS-like Tyrosine Kinase 3-internal Tandem Duplication-mutated Acute Myeloid Leukemia. Chin Med J 2016;129:2512-3.
Diagnosis of subacute thyroiditis is mainly based on clinical features and laboratory findings such as typical neck pain, diffuse swelling of the thyroid gland, altered thyroid function, and depressed radioactive iodine intake. This case showed typical clinical symptoms and imaging findings, no indication of infection, and a good response to glucocorticoids, which suggested a diagnosis of subacute thyroiditis.

Subacute thyroiditis is usually caused by immune attack, which may be associated with autoimmune disease, infection, or drugs. In the present case, no evidence of bacterial or viral infection was found, and the level of autoimmune antibodies remained normal. Thus, drug-induced was suspected. It has been proposed that tyrosine kinase inhibitor (TKI)-related thyroid dysfunction is caused by thyroiditis, which causes inhibition of iodide uptake, reduced synthesis of thyroid hormone, impaired thyroid blood flow, and ischemia. However, the mechanism by which sorafenib-induced thyroid dysfunction occurs is unknown. One hypothesis is that sorafenib inhibits vascular endothelial growth factor (VEGF) signal transduction, which may lead to regression of the thyroid capillary bed.[1] In this hypothesis, sorafenib as a VEGF receptor inhibitor could affect thyroid function by preventing the binding of VEGF to normal thyroid cells and/or by impairing thyroid blood flow, resulting in thyroiditis and thyroid dysfunction. This anti-angiogenic effect results in reduced tumor growth and improved survival of mice. Sorafenib also seems to decrease proliferation and survival of tumor cells by blocking the RAF/MEK/ERK pathway.[2] These combined actions can explain the antitumoral activity of sorafenib. In future studies, thyroid gland biopsy and molecular investigations will be necessary to help clarify the mechanism of sorafenib-induced thyroid dysfunction.

There are few guidelines on the frequency of thyroid function monitoring during TKIs treatment. Wolter et al. proposed measuring thyroid-stimulating hormone (TSH) on day 1 and 28 of the first four cycles of sunitinib as thyroid dysfunction has been shown to develop early during therapy when it occurs. They also suggested that patients with normal TSH values after the first four cycles can have TSH measured on day 28 of every three cycles. Mannavola et al. even suggested thyroid function should be followed after cessation of TKI therapy.[3]

In conclusion, subacute thyroiditis is an uncommon side effect of sorafenib when treating FLT3-positive AML. Early withdrawal of sorafenib and the use of glucocorticoids may protect the thyroid gland from functional impairment.

Financial support and sponsorship
The study was supported by the grant from the National Natural Science Foundation of China (No. 81372031).

Conflicts of interest
There are no conflicts of interest.

References
1. Konca Degertekin C, Coskun U, Balos Törüner F, Aktürk M, Demirci U. Hyperthyroidism and thyroid autoimmunity induced by sorafenib in metastatic renal cell cancer. Endocrine 2012;42:756-7. doi: 10.1007/s12020-012-9683-2.
2. Li L, Wang Y, Zhao Y, Zou S, Lin M, Yu X, et al. Evaluation with low-dose dual-phase helical computed tomography of patients with thyroid lesions. Chin Med J 2014;127:3937-43. doi: 10.3760/cma.j.issn.0366-6999.20141569.
3. Tamaskar I, Bukowski R, Elson P, Ioachimescu AG, Wood L, Dreicer R, et al. Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. Ann Oncol 2008;19:265-8. doi: 10.1093/annonc/mdn483.
4. Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006;66:11851-8. doi: 10.1158/0008-5472.CAN-06-1377.
5. Mannavola D, Coco P, Vannucchi G, Bertelli R, Carletto M, Casali PG, et al. A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. J Clin Endocrinol Metab 2007;92:3531-4. doi: 10.1210/jc.2007-0586.