Investigation of Regorafenib-induced Hypothyroidism in Patients with Metastatic Colorectal Cancer

KAZUO SUGITA¹, KAZUYOSHI KAWAKAMI¹, TAKASHI YOKOKAWA¹, YUTARO MAE¹, WATARU TOYA¹, AKANE HAGINO¹, KENICHI SUZUKI¹, MITSUKUNI SUENAGA², NOBUYUKI MIZUNUMA², TOSHIHARU YAMAGUCHI² and TOSHIHIRO HAMA¹

Departments of ¹Pharmacy and ²Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan

Abstract. Hypothyroidism is one of the side-effects caused by regorafenib. In the Japanese subset of the CORRECT study, hypothyroidism developed in 1.5% of the patients, but was not grade 3 or higher in any patient. Regorafenib is an oral multi-kinase inhibitor that has the same mechanism of action as sunitinib. However, the reported incidence of sunitinib-related hypothyroidism varies widely, ranging from 16.0% in clinical trials to 35.4% in post-marketing surveillance studies. In general, symptoms of hypothyroidism include fatigue and dysphonia. Hyperthyroidism must, therefore, be appropriately managed in order to maintain patient quality of life and avoid a critical level of hypothyroidism. During the first cycle of treatment with regorafenib, the incidence of abnormal thyroid-stimulating hormone (TSH) elevation was 31.4%. Our results suggest that thyroid function tests should be performed from day 1 of treatment with regorafenib. It would be prudent to consider routine monitoring of thyroid function in all patients who receive regorafenib and to recommend endocrinological consultation as necessary.

Regorafenib is a novel oral multi-kinase inhibitor that blocks the activity of several protein kinases involved in the multiple biological processes for progression and development of cancer; these kinases include vascular endothelial growth factor receptor (VEGFR) 1-3 and tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2) involved in tumor angiogenesis, KIT, rearranged during transcription tyrosine kinase (RET), rat fibroblastoma 1 (RAF1), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) in oncogenesis, and platelet derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) in the tumour microenvironment (1).

Hypothyroidism is one of the side-effects caused by regorafenib. In the Japanese subset of the CORRECT study, hypothyroidism developed in 1.5% of the patients, but was not grade 3 or higher in any patient (2). Regorafenib is an oral multi-kinase inhibitor that has the same mechanism of action as sunitinib. However, the reported incidence of sunitinib-related hypothyroidism varied widely, ranging from 16.0% in clinical trials to 35.4% in postmarketing surveillance studies (3, 4). An association between sunitinib treatment and thyroid dysfunction has also been reported by other groups (5-7).

Symptoms of hypothyroidism include fatigue and dysphonia. Hyperthyroidism must, therefore, be appropriately managed in order to maintain patient quality of life and avoid a critical level of hypothyroidism. In the present study, we clarified the frequency and time of onset of hypothyroidism to improve the management of this side-effect of regorafenib.

Patients and Methods

Patients. This single-Center, retrospective study included patients who received regorafenib at the Japanese Foundation for Cancer Research, Cancer Institute Hospital. Between May 1, 2013 and November 30, 2014, a total of 64 patients received regorafenib for the treatment of metastatic colorectal cancer. Patients with abnormal results of thyroid function tests (TFTs) at baseline (before initiation of regorafenib) and those who had previously received thyroid hormone replacement therapy because of underlying thyroid disease were excluded from the study. All patients initially received 160 mg regorafenib (Bayer, Leverkusen, Germany) once daily for the first three weeks of each 4-week cycle. Doses were adjusted on the basis of haematological and non-haematological adverse events in accordance with the manufacturer’s recommendations.

Evaluation of thyroid function. All patients routinely underwent TFTs on day 0 (every treatment cycle), day 21, and at the time of confirming disease progression during treatment with regorafenib.
The test variables included serum thyroid-stimulating hormone (TSH), serum free thyroxine (FT4), and serum free triiodothyronine (FT3). Our laboratory reference normal ranges are 0.30-3.68 mU/l for TSH, 0.92-1.45 ng/dl for FT4, and 1.81-3.33 pg/ml for FT3. We retrospectively analysed the frequencies and onset times of abnormal TSH elevations. All study protocols were approved in advance by the Institutional Review Board of the hospital (approval number: 2014-1023).

Definition of hypothyroidism. The biochemical diagnosis of sub-clinical hypothyroidism was performed in accordance with the guidelines of the Japan Thyroid Association (8). Sub-clinical hypothyroidism was defined as a serum TSH level above the upper limit of normal, with FT4 and FT3 within normal limits. Clinical hypothyroidism was defined as a low serum FT4 accompanied by an elevated TSH level. The treating physician determined whether thyroid hormone replacement therapy should be initiated in patients who had serum TSH levels of >10 mU/l.

Results

Patient’s characteristics. In total, 35 out of 64 patients were eligible for evaluation. The 29 patients who were excluded from the study had abnormal TFT results at baseline. The demographic characteristics of the 35 eligible patients are presented in Table I. In the study group as a whole, the median TSH level at baseline was 1.76 mU/l (range=0.61-3.67 mU/l), which was within our laboratory reference range.

Thyroid function during regorafenib treatment. Table II summarizes the TFT results during regorafenib treatment. Only 20 patients (57.1%) had no biochemical thyroid abnormality. Twelve patients (42.8%) had one or more episodes of elevated TSH level, and three patients (8.5%) had sub-clinical hypothyroidism requiring treatment. The highest TSH level observed was 18.75 mU/l, equivalent to approximately 5.0-fold the upper limit of normal. Thyroid function abnormalities were detected relatively early during treatment: the median time to an abnormal TSH level was 21 days (Figure 1). Abnormal elevations of TSH were noted in 31.4% of the patients during the first cycle of regorafenib.

Discussion

Our study prospectively analyzed the incidence of hypothyroidism in patients with cancer who received regorafenib. After initiation of regorafenib, one-third of the patients had no biochemical TFT abnormalities. Hypothyroidism requiring treatment developed in 2.8% of the patients. The biochemical TFT abnormalities in these patients improved in response to treatment with 25 μg/day of levothyroxine sodium hydrate. For instance, in one patient the TSH level improved from a high of 16.9 mU/l to a normal 2.44 mU/l with 25 μg/day of levothyroxine sodium hydrate.

Because all patients had normal thyroid function at baseline, the following percentages apply to new-onset hypothyroidism. There was a gap between the 3.0% incidence of hypothyroidism caused by regorafenib in the CORRECT study (2) and the 5.7% incidence in our study. There was also a major gap between the 1.4% incidence of abnormal elevations of TSH caused by regorafenib in the CORRECT study (2) and the 42.8% incidence in our study. We attribute the high frequency of abnormal TSH elevations in our study to the fact that all patients routinely underwent TFTs on day 21 during treatment with regorafenib.
At the onset of the second cycle, 37.1% of patients had abnormal elevations of TSH. There was a low incidence of abnormal elevations of TSH after the third cycle because nearly all patients required a reduction in the dose of regorafenib within the first two cycles.

Hypothyroidism is uncommon in the general population, with a prevalence of 4% to 8.5% (9, 10). Reliable data on the prevalence of hypothyroidism in patients with cancer are not available; however, some preliminary data suggest a slightly higher frequency of hypothyroidism in patients with specific tumor types, such as melanoma and breast cancer (11, 12). In general, hypothyroidism is particularly common among the elderly and women (13). However, in our study, the median patient age was 65 (range=44-78) years and the male to female ratio was 3:2, suggesting that these patient characteristics did not contribute substantially to the observed incidence of hypothyroidism in our study. The clinical features of patients with hypothyroidism are highly variable and non-specific, and side-effects of regorafenib can be very similar to symptoms of hypothyroidism, especially in patients with advanced cancer. Therefore, we cannot definitively determine whether fatigue in patients receiving regorafenib is caused by hypothyroidism.

The molecular mechanisms of regorafenib-induced hypothyroidism remain unclear. Regorafenib may have a direct effect on the thyroid gland by, for example, inhibiting VEGFR, PDGFR, or both. Recent studies in a mouse model have shown that VEGFR inhibition can induce capillary regression in various organs, including the thyroid. Moreover, the vasculature of the thyroid showed the greatest regression of all organs (14, 15). Remarkably, in this animal model, thyroid capillaries regenerated in the absence of VEGFR inhibition. It is interesting that in these studies by Baffert et al. and Kamba et al., TSH also increased in mice treated with VEGF inhibitors. Indirectly, regorafenib may affect the thyroid by interfering with the metabolism of T4/T3 hormones or with the action of thyroid hormone at the pituitary level. In patients who receive sorafenib, another tyrosine kinase inhibitor, thyroid dysfunction is apparently not a frequent side-effect (16).

In our study, patients in whom sub-clinical hypothyroidism developed and required treatment showed early elevation of TSH, occurring at a median of three weeks after the initiation of regorafenib therapy. We, thus, recommend that all patients who receive regorafenib undergo TFTs during the first treatment cycle. Application of intensive initial screening is expected to facilitate the early detection of patients who are at risk for regorafenib-induced thyroid dysfunction after initiation of treatment. We also recommend that patients with a TSH level of >10 mU/l and either a low T4 or a normal T4 level associated with typical symptoms of hypothyroidism should receive hormone replacement therapy. Because the TSH level declines and potentially normalizes by the end of the one-week rest period per cycle of regorafenib, the decision of whether to start hormone replacement therapy should be based on the TSH level on day 1 of the next cycle rather than day 21 of the current cycle in order to avoid overtreatment.

In conclusion, it is important that clinicians consider potential adverse effects of regorafenib on thyroid function. Regorafenib-induced hypothyroidism is easily manageable by hormone replacement therapy and should not discourage the use of regorafenib indicated for cancer treatment. Hormone replacement is necessary not only to reduce symptoms of hypothyroidism, such as fatigue, but also to avoid the potentially life-threatening complications of severe hypothyroidism, such as myxoedema coma.

We conclude that our management protocol for hypothyroidism in patients receiving regorafenib should be validated in a further prospective randomized trial, and hope that our data will help clinicians in clinical practice.

References


Table II. Thyroid function characteristics of patients treated with regorafenib (n=35).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with abnormal TSH elevation</td>
<td>15 (42.8)</td>
</tr>
<tr>
<td>Maximal TSH level (mU/l), n (%)</td>
<td></td>
</tr>
<tr>
<td>3.68-9.99</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>10.00 or higher</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Patients receiving levothyroxine sodium hydrate, n (%)</td>
<td>3 (8.5)</td>
</tr>
<tr>
<td>Patients with abnormal FT4 decrease, n (%)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Patients with abnormal FT3 decrease, n (%)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Patients with hypothyroidism, n (%)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Patients with sub-clinical hypothyroidism, n (%)</td>
<td>13 (37.1)</td>
</tr>
</tbody>
</table>

TSH: Thyroid stimulating hormone; FT3/4: Free triiodothyronine/Free thyroxine


10 Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS and Weissman NJ: Sub-clinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291: 228-238, 2004.


