Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 61; Numer/Number 5/2010
ISSN 0423–104X

Treatment with sorafenib in advanced thyroid cancer — a case report

Leczenie sorafenibem w zaawansowanym raku tarczycy — opis przypadku

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Abstract

Papillary thyroid cancer (PTC) usually has a good prognosis. The treatment, including total thyroidectomy and complementary radioiodine (RAI) therapy, gives complete remission in 90% of patients. However, in 10% of subjects with metastatic disease, the prognosis is poor. In the group of patients with disease progression and no ^{131}I uptake, searching for new therapeutic modalities before all tyrosine kinase inhibitors and other antiangiogenic agents is necessary.

The study presents the case of a 55-year-old male with advanced PTC /pT3mNxMo/ diagnosed in 1993. Primary treatment by total thyroidectomy and ^{131}I ablation led to complete remission. In 2000 local as well as lymph node recurrence was diagnosed and successively treated by surgery. In 2006 an increasing serum thyroglobulin level was noted and a single lung metastasis was diagnosed and operated on. In 2007 new foci in CNS and vertebral column with no ^{131}I uptake were stated. Further progression (bones, CNS, and pterygoid muscle) was confirmed by PET-CT. The patient underwent neurosurgical metastasectomy twice and palliative CNS and vertebra's radiotherapy. Liver metastases were diagnosed in 2009. Treatment with increasing doses of thalidomide (up to 800 mg/d) was administered for 3 months with a good tolerance; however, the therapy was withdrawn due to cancer progression. Next, sorafenib (800 mg/d) was given for 16 weeks. Radiological examination performed after 16 weeks confirmed stable disease, whereas 2 months later, after sorafenib withdrawal due to lack of treatment possibility, further progression was observed. Metronomic chemotherapy with Adriamycin was instituted which gave disease stabilization for 6 months. The patient died with advanced disseminated disease due to pulmonary embolism.

We present this case to document no adverse effects of therapy with sorafenib in a patient with brain DTC metastases. Sorafenib therapy was only short-term, but no progression occurred in this time. **(Pol J Endocrinol 2010; 61 (5): 492–496)**

Key words: *differentiated thyroid cancer, sorafenib, radioiodine resistant*

Streszczenie

Rak brodawkowaty tarczycy należy do nowotworów o dobrym rokowaniu. Terapia oparta na całkowitym wycięciu tarczycy i uzupełniającym leczeniu jodem promieniotwórczym u 90% pacjentów prowadzi do całkowitej remisji choroby nowotworowej. U około 10% chorych, u których dochodzi do rozsiewu raka, rokowanie jest niepomyślne. U chorych, z rozsiewem raka, u których ogniska nowotworu nie wykazują zdolności wychwytu ^{131}I konieczne jest poszukiwanie nowych możliwości terapeutycznych. W tym kontekście rozważa się zastosowanie leków antyangiogennych, w tym inhibitorów kinaz tyrozynowych.

W pracy przedstawiono przypadek 55-letniego pacjenta z rozpoznaniem zaawansowanego raka brodawkowatego tarczycy/pT3mNxMo leczonego od 1993 roku, u którego w terapii zastosowano inhibitor angiogenezy (talidomid) i kinaz tyrozynowych (sorafenib). Leczenie pierwotne, dwuetapowe całkowite wycięcie tarczycy w 1994 i uzupełniające leczenie ^{131}I (60 mCi) w 1994 roku doprowadziło do remisji choroby nowotworowej. W 2000 chory przebył operacyjne usunięcie wznowy miejscowej i przerzutów do węzłów chłonnych. W 2006 roku, w toku diagnostyki narastającej hipertyreoglobulinemii rozpoznano przerzut do płuca prawego, który usunięto operacyjnie. W 2007 roku stwierdzono niejodochwytny przerzut do kręgosłupa i ośrodkowego układu nerwowego (OUN). Kontrolne badania obrazowe, w tym PET-CT, potwierdziły dalszą progresję raka pod postacią nowych ognisk przerzutowych w OUN, kośćcu i mięśniu skrzydłowym. Chory przebył 2-krotne operacyjne usunięcie zmian ogniskowych w OUN, paliatywną radioterapię OUN i paliatywną radioterapię przerzutu do kręgosłupa. W 2009 roku rozpoznano przerzuty do wątroby. W dalszej terapii stosowano talidomid we wzrastającej dawce do 800 mg/d. przez okres 3 miesięcy, co nie zapobiegło dalszej progresji. Następnie chory otrzymywał sorafenib w dawce 800 mg/d. przez okres 16 tygodni. Badania obrazowe wykonane po 16 tygodniach terapii potwierdziły stabilizację choroby nowotworowej, natomiast 2 miesiące po odstawieniu leku ze względu na brak możliwości kontynuacji terapii doszło do dalszej progresji. Następnie chory otrzymywał przez okres 6 miesięcy metronomiczną chemioterapię (adriblastyna), która doprowadziła do stabilizacji choroby. Chory zmarł w stadium zaawansowanego raka tarczycy z powodu zatorowości płucnej.

Wniosek: W prezentowanym przypadku chorego na raka brodawkowatego tarczycy z przerzutami do mózgu, terapia sorafenibem nie spowodowała żadnych powikłań, a w czasie 16 tygodni jej stosowania obserwowano stabilizację zaawansowanej choroby nowotworowej. **(Endokrynol Pol 2010; 61 (5): 492–496)**

Słowa kluczowe: *zróżnicowany rak tarczycy, sorafenib, odporność na radiojod*

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Introduction

Differentiated thyroid cancers (DTC) derive from follicular cells. Molecular pathogenesis of the most frequent histotype, papillary thyroid cancer (PTC), is related to constitutive activation of the Ras-Raf-MEK-MAP-ERK kinase signalling pathway due to B-Raf mutations, Ras mutations, or to RET/PTC rearrangement [1–4]. B-Raf^{V600E} is the most common genetic alteration in PTC (29–83%) and plays a crucial role in cell proliferation, survival, and de-differentiation. B-Raf^{V600E} is associated with more aggressive PTC phenotype and is more frequently observed in subjects with extra-thyroidal extension or higher clinical stage [1, 2]. Gain-of-function mutations of RAS occur in about 15% of PTC. Rearrangements of RET (RET/PTC) occur in 5–30% of spontaneous cases and in 60–70% of radiation-induced PTC [5]. Vascular endothelial growth factor (VEGF) is involved in thyroid carcinogenesis, where overexpression of VEGF and PDGF is observed [2].

Differentiated thyroid cancers are usually characterized by a good prognosis. The 10-year relative survival rates for subjects with PTC, follicular thyroid cancer (FTC) and Hurthle cell carcinomas assessed on the basis of a large report on 53,856 cases of thyroid carcinoma were 93%, 85%, and 76%, respectively [6]. Depending on initial therapy and other prognostic factors, cancer recurrences are diagnosed in about 30% of DTC patients, in most of them during the first decade after primary treatment [7]. About 10–20% of DTC patients develop distant metastases. Approximately 50% of them die of cancer [7]. The treatment of choice in patients with local cancer relapse (thyroid bed or lymph-node metastases), particularly if distant metastases are not present, is surgical excision, when possible, followed by radioiodine therapy and/or external beam radiation if necessary [8]. In cases with functional distant metastases, conventional therapy is based on radioiodine (RAI). However, about 50% of them do not respond to RAI due to lack of ^{131}I uptake or progression in spite of adequate RAI doses [9]. In this group of patients with disease progression resistant to ^{131}I, new therapeutic modalities are necessary. Among antiangiogenic agents, thalidomide and its derivates and, more importantly, tyrosine kinase inhibitors are considered to target tumour angiogenesis.

Thalidomide is an anti-inflammatory, anti-angiogenic, and immunomodulatory agent successfully used for the therapy of multiple myeloma. It reduces activity of TNF-α by degradation of its mRNA and inhibits angiogenesis by its influence on vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Its immunomodulatory effect is related to repression of COX-2 and cytokines [10]. Recently its derivate lenalidomide is increasingly used for inhibition of angiogenesis in malignant tumours.

Sorafenib is a multikinase inhibitor targeting both tumour cells and tumour vasculature [11]. It was initially developed as a selective inhibitor of Raf-1, a member of the Raf/MEK/ERK signalling pathway. Subsequently, its activity against B-Raf (wild type as well as mutant B-Raf^{V600E}), vascular endothelial growth factor receptor-2 and -3 (VEGFR-2, VEGFR-3), platelet-derived growth factor receptor (PDGFR), Fms-like thyrosine kinase 3 (Flt-3), stem-cell growth factor (c-KIT), and FGFR-1 was demonstrated [11, 12]. Due to this activity, the drug influences division and growth of tumour cells and potentiates cellular apoptosis and simultaneously exerts an antiangiogenic effect by inhibition of VEGFR2. Carlomagno et al. showed that sorafenib inhibits the enzymatic function of RET/PTC fusion protein [13].

Sorafenib has already been approved by the FDA for patients with metastatic renal cell carcinoma as well as in unresectable hepatocellular cancer. Currently it is under evaluation for other malignancies such as melanoma and thyroid cancer [14, 15]. In 2008 the National Comprehensive Cancer Network, after promising initial preclinical and clinical studies, recommended the use of sorafenib in the management of progressive, iodine-refractory PTC [2].

Case report

We present the case of a 55-year-old male with advanced, RAI refractory PTC treated with antiangiogenic factor (thalidomide) and subsequently with multikinase inhibitor (sorafenib). PTC was diagnosed after resection of thyroid right lobe and isthmus due to a cold nodule in November 1993. Initial pathology revealed extrathyroidal invasion with infiltration of adjacent muscles /pT3aNxM0. Reoperation (total resection of the thyroid gland) was carried out two months later in January 1994 followed by RAI thyroid ablation (60 mCi ^{131}I) in March 1994. Whole body scintigraphy (WBS) performed 72 hours after ^{131}I administration showed tracer uptake in the thyroid bed only. Stimulated serum thyroglobulin (Tg) was within the normal range — 2.11 ng/mL (Tg recovery 105%). Surgical treatment was complicated by hypoparathyroidism and paresis of the left recurrent nerve. Local recurrence in the thyroid bed was diagnosed during neck sonography in November 1999. At this time, during thyroxine withdrawal, serum Tg concentration increased to 11.98 ng/mL. Surgical resection was carried out in May 2000. Diagnostic procedures performed in July 2000 confirmed complete remission: neck US was normal, WBS revealed no pathological ^{131}I uptake, stimulated serum Tg level decreased to 0.24 ng/mL, and Tg recovery 88%. A lung metastasis was diagnosed

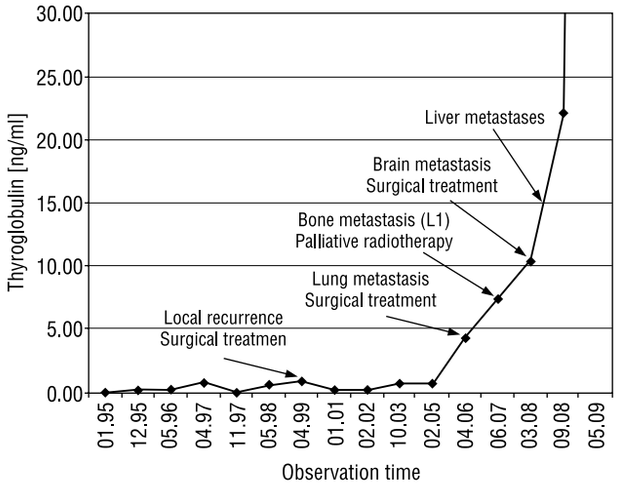

Figure 1. *Serum Tg measurements (on LT4) during the observation*
Rycina 1. *Stężenie tyroglobuliny w trakcie obserwacji*

by X-ray examination and confirmed by PET/CT in October 2006. The first signal of this relapse was increased serum Tg level noticed 6 months earlier (Fig. 1). The patient underwent metastasectomy in January 2007 with subsequent ^{131}I treatment in March 2007. 100 mCi ^{131}I was given after rhTSH administration. WBS showed no ^{131}I uptake, serum Tg was 10.6 ng/mL (Tg recovery 98%). Further cancer progression was stated in July 2007 on the basis of elevated Tg concentration (77.6 ng/mL; Tg rec. 101% after rhTSH) and PET-CT (focal tracer uptake in vertebral column — L1). Palliative radiotherapy (8 Gy/ /tumour) was carried out. However, there was no possibility of ^{131}I therapy because WBS was negative (Fig. 2). In January 2008 a new metastatic lesion in the central nervous system was diagnosed and surgically removed. Another brain metastasis (Fig. 3) as well as new lesions in pterygoid muscle and bones were found in PET-CT performed 3 months later (Fig. 4). The patient underwent the second surgical resection of brain metastasis in April 2008 followed by palliative radiotherapy of the central nervous system (total dose 20 Gy/tumour) due to further progression in September 2008. Successive CT and MRI examinations revealed gradual enlargement of known metastases (in the central nervous system, pterygoid muscle, and bones) as well as a new lesion localized in the liver. Serum Tg level, assessed on thyroxin (LT4) suppressive therapy, gradually increased from 57 ng/mL in October 2007 to 171.8 ng/mL in March 2009. Treatment with increasing doses of thalidomide (from 200 mg/d up to 800 mg/d) was administered between March and June 2009 with a good tolerance, without any adverse events. The drug was discontinued due to cancer progression observed in CNS. At the end of this period the Tg level (on LT4) rose to 1800 ng/mL.

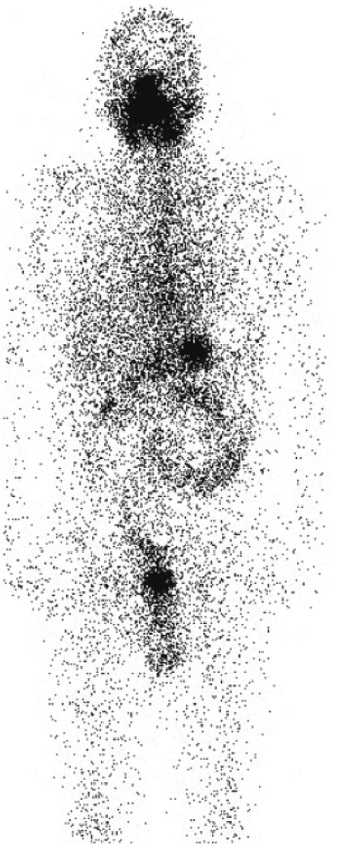

Figure 2. *Whole body scintigraphy performed after ^{131}I treatment in March 2007. No pathological ^{131}I uptake was observed*
Rycina 2. *W scyntygrafii całego ciała wykonanej po leczeniu ^{131}I w marcu 2007 nie stwierdzono patologicznego wychwytu radioznacznika*

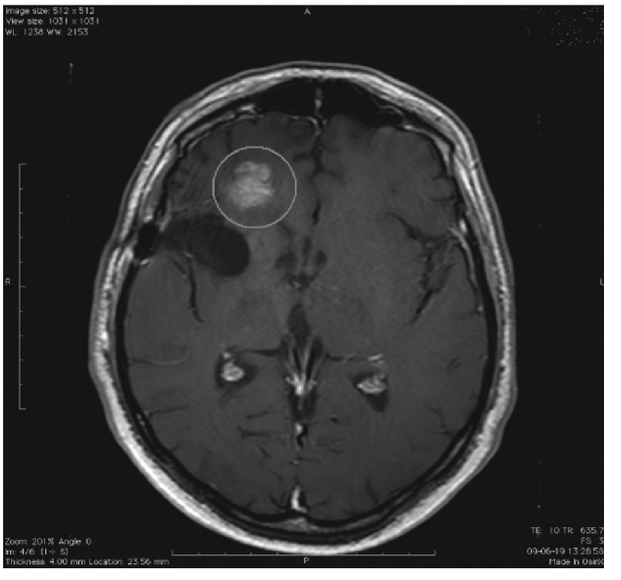

Figure 3. *A brain metastasis localized in the right frontal lobe*
Rycina 3. *Przerzut raka tarczycy do mózgu zlokalizowany w płacie czołowym po stronie prawej*

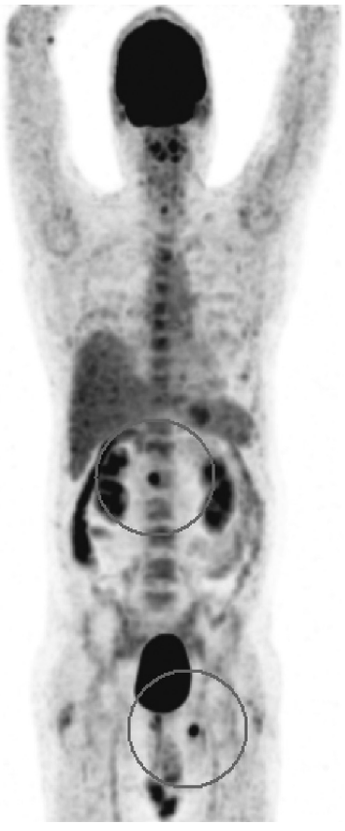

Figure 4. *PET-CT performed in June 2007 confirmed bone metastases (vertebral column L1 and pelvis)*

Rycina 4. *Badanie PET-CT wykonane w czerwcu 2007 potwierdziło obecność przerzutów do kośćca (kręgosłup — L1 i miednica)*

Next, sorafenib therapy (800 mg/d) was instituted. The tolerance was good. No adverse events were observed. CT and MRI examinations performed after 16 weeks confirmed stable disease. However, the treatment was withdrawn due to an administrative reason (non-refundable costs). Radiological examinations carried out two months later revealed further progression (lung and bones). Then metronomic chemotherapy (Adriblastin 40 mg/m^2) was given with a good therapeutic effect — stable disease. Unfortunately, the patient died due to pulmonary embolism in July 2010.

Discussion

Standard therapy in patients with metastatic thyroid cancer is based on surgical resection and radioiodine treatment. For subjects not amenable to surgery and ^{131}I therapy, searching for new therapeutic modalities is necessary. External beam radiotherapy plays an important role in local disease control as well as in a palliative treatment of distant metastases, particularly in brain, bones, and mediastinum. Conventional chemotherapy is relatively ineffective and should be reserved for patients with rapid progression, when other options are not available [8, 16, 17].

In our PTC patient, initial treatment based on total thyroidectomy and ^{131}I ablation led to complete remission. Progressive disease was stated 12 years after initial cancer diagnosis. Increasing serum thyroglobulin level was the first signal of the relapse, and then radiological examination showed at first a lung metastasis and subsequently new lesions localized in CNS, vertebral column, soft tissues, lungs, and liver. Due to lack of uptake, RAI therapy was not possible. Treatment with increasing doses of thalidomide (up to 800 mg/d) had been administered in 2009 for 3 months with a good tolerance but was withdrawn due to cancer progression confirmed by the RECIST criteria.

The rationale for the use of thalidomide in advanced DTC is related to its anti-angiogenic and immunomodulatory properties. A phase II clinical trial published in 2007 assessed the efficacy of thalidomide in patients with metastatic, progressive, RAI refractory thyroid cancer. 28 of 36 subjects with various histological thyroid cancer subtypes (follicular, papillary, insular, and medullary thyroid carcinoma) treated with thalidomide (median maximum daily dose of about 600 mg) were evaluated. 18% achieved a partial response and 32 % had stable disease with median duration 4 (range 2–6 months) and 6 months (range 2–14 months), respectively. Median survival for responders was 23.5 months and 11 months for non-responders [10]. Unfortunately, this treatment was not effective in our patient. Thus, treatment with sorafenib was considered.

Sorafenib has been evaluated in multiple phase I and II studies in different tumour types [11, 18]. Its activity against Raf-1, B-Raf (both wild and mutant B-Raf^{V600E} types), VEGFR-2, VEGFR-3, PDGFR as well as enzymatic function RET/PTC fusion protein justify its use in patients with thyroid cancer. Sorafenib inhibited the *in vitro* proliferation of cell lines of anaplastic thyroid cancer (ATC) and showed significant antitumor activity in an orthotopic xenograft model of ATC [19]. Due to its anti-RET activity, sorafenib was also investigated as potential therapeutic agent in patients with medullary thyroid cancer (MTC) [14, 20–23]. Two phase II clinical trials published in 2008–2009 demonstrated its effectiveness in advanced, RAI refractory DTC [14, 15]. In the first study among 30 patients (18-PTC, 9-FTC, 1 MTC and 2 ATC) with progressive disease treated with sorafenib for a median 27 weeks, partial response (PR) and stable disease (SD) were achieved in 23% and 53% of patients, respectively. The median PFS (progression-free survival) was 79 weeks [14]. In the second trial, which enrolled 41 PTC subjects, clinical benefit was observed in 71% of patients (15% PR, 56% SD). Median duration

of PR and PFS were 7.5 and 15 months, respectively [15]. In 2010 Cabanillas et al. reported their experience in 15 progressive, RAI-refractory DTC patients. Sorafenib was administered to 13 of them, whereas in the remaining two Sunitinib was given. Response rates were comparable to previous studies — PR in 20% and SD in 60% patients with median PFS duration of 19 months [12]. There was also a successful attempt of the use of sorafenib in paediatric PTC. A 14-year-old girl with progressive lung metastases of PTC achieved significant improvement after 67-day therapy. After treatment withdrawal, minimal progression was observed, but the second sorafenib course was similarly effective and led to a clinical response [24].

Sorafenib (800 mg/d) was given to our patient for 16 weeks. Radiological examination performed after that time confirmed stable disease both for brain as well as other soft tissue and bone metastases. However, due to a lack of treatment possibility, the drug was discontinued and two months later further cancer progression was confirmed by CT examination.

We present this patient for two reasons: firstly to document no adverse effects of therapy with sorafenib in a patient with brain metastases, and secondly to show its effectiveness in the stabilization of DTC in patients with advanced, radioiodine-refractory disease.

References

1. Nucera C, Goldfarb M, Hodin R et al. Role of B-Raf(V600E) in differentiated thyroid cancer and preclinical validation of compounds against B-Raf(V600E). Biochim Biophys Acta 2009; 1795: 152–161.
2. Woyach JA, Shah MH. New therapeutic advances in the management of progressive thyroid cancer. Endocr Relat Cancer 2009; 16: 715–731.
3. Deshpande HA, Gettinger SN, Sosa JA. Targeted therapy for thyroid cancer: An updated review of investigational agents. Curr Opin Investig Drugs 2010; 11: 661–668.
4. Fagin JA. How thyroid tumors start and why it matters: kinase mutants as targets for solid cancer pharmacotherapy. J Endocrinol 2004; 183: 249–256.
5. Lanzi C, Cassinelli G, Nicolini V et al. Targeting RET for thyroid cancer therapy. Biochem Pharmacol 2009; 77: 297–309.
6. Hundahl SA, Fleming ID, Fremgen AM et al. A National Cancer Data Base Report on 53,856 Cases of Thyroid Carcinoma Treated in the U.S. 1985–1995. Cancer 1998; 83: 2638–2648
7. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994; 97: 418–428.
8. Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Thyroid. 2009; 19: 1167–1214.
9. Durante C, Haddy N, Baudin E et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006; 91: 2892–2899.
10. Ain KB, Lee C, Williams KD. Phase II trial of thalidomide for therapy of radioiodine-unresponsive and rapidly progressive thyroid carcinomas. Thyroid 2007; 17: 663–670.
11. Ratain MJ, Eisen T, Stadler WM et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006; 24: 2505–2512.
12. Cabanillas ME, Waguespack SG, Bronstein Y et al. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab 2010; 95: 2588–2595.
13. Carlomagno F, Anaganti S, Guida T et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 2006; 98: 326–334.
14. Gupta-Abramson V, Troxel AB, Nellore A et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 2008; 26: 4714–4719.
15. Kloos RT, Ringel MD, Knopp MV et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 2009; 27: 1675–1684.
16. Haugen BR, Kane MA. Approach to the thyroid cancer patient with extracervical metastases. J Clin Endocrinol Metab 2010; 95: 987–993.
17. Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. J Clin Endocrinol Metab 2009; 94: 1493–1499.
18. Hong DS, Sebti SM, Newman RA et al. Phase I trial of a combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in advanced malignancies. Clin Cancer Res 2009; 15: 7061–7068.
19. Kim S, Yazici YD, Calzada G et al. Sorafenib inhibits the angiogenesis and growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice. Mol Cancer Ther 2007; 6: 1785–1792.
20. Cakir M, Grossman AB. Medullary thyroid cancer: molecular biology and novel molecular therapies. Neuroendocrinology 2009; 90: 323–348.
21. Hong D, Ye L, Gagel R et al. Medullary thyroid cancer: targeting the RET kinase pathway with sorafenib/tipifarnib. Mol Cancer Ther 2008; 7: 1001–1006.
22. Lam ET, Ringel MD, Kloos RT et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol 2010; 28: 2323–2330.
23. Sugawara M, Geffner DL, Martinez D et al. Novel treatment of medullary thyroid cancer. Curr Opin Endocrinol Diabetes Obes 2009; 16: 367–372.
24. Waguespack SG, Sherman SI, Williams MD et al. The successful use of sorafenib to treat pediatric papillary thyroid carcinoma. Thyroid 2009; 19: 407–412.