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CASE REPORT AND REVIEW

Partial remission of metastatic papillary thyroid carcinoma with sunitinib. Report of a case and review of the literature

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Abstract Tyrosine kinase receptors have been implicated in thyroid cancer. Therefore, tyrosine kinase inhibitors may be used for the treatment of advanced metastatic thyroid carcinoma. The aim is to present a case of metastatic papillary thyroid carcinoma responding to the administration of sunitinib, a multi-targeted protein kinase inhibitor. A patient presented with metastatic papillary thyroid carcinoma and hyperthyroidism. After euthyroidism was achieved the patient was treated by the administration of therapeutic radioiodine ^{131}I, radiotherapy and sunitinib, a multi-targeted tyrosine kinase inhibitor. Thyroglobulin levels decreased from 9,594 to 6,816 ng/ml after 1 month, 6 months later being 2,776 ng/ml. The lesion in the pelvis was 12.5 × 9 cm before treatment decreasing thereafter and the patient improved clinically. The administration of sunitinib resulted in partial disease response in a patient with progressive metastatic papillary thyroid carcinoma. Protein kinase inhibitors may prove useful in the management of advanced metastatic papillary thyroid carcinoma.

Keywords Papillary thyroid cancer · Sunitinib · Tyrosine kinase inhibitors · Metastatic thyroid carcinoma

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Introduction

Carcinoma of the thyroid is the most common endocrine malignancy and its incidence continues to grow [1, 2]. Differentiated thyroid cancer, which includes papillary and follicular thyroid cancer subtypes accounts for 90% of thyroid malignancies. Fortunately, most patients with differentiated thyroid cancer do well with traditional therapy, which includes total thyroidectomy, radioiodine ablation, and thyroid hormone suppression [3]. In the past, few effective treatment options were available for patients with advanced thyroid cancer [4–6]. Advances in our understanding of the molecular basis of thyroid cancer initiation and progression have led to new potential therapies targeted at specific molecular pathways [7–9]. Activation of tyrosine kinase receptors has been implicated in thyroid cancer [10, 11]. Therefore, inhibition of these receptors may serve as potential targets for anticancer therapy [12]. Sunitinib is an oral small molecule, multi-targeted receptor tyrosine kinase inhibitor [13] that is used successfully for the treatment of metastatic renal cell carcinoma [14] and imatinib-resistant gastrointestinal stromal tumors [15]. The case of a patient with metastatic thyroid carcinoma is presented who responded to the administration of sunitinib, a novel multiple kinase inhibitor.

Case report

A 46-year-old male patient underwent thyroid lobectomy for a large benign thyroid adenoma of embryonic origin. Substitution therapy with thyroxine 125 μg daily was administered. Seven years later he presented with hyperthyroidism, free T_4 being 35.9 pmol/l (9.1–23.8 pmol/l), free T_3 12 pmol/l (3.4–8.5 pmol/l), and TSH 0.1 mU/l

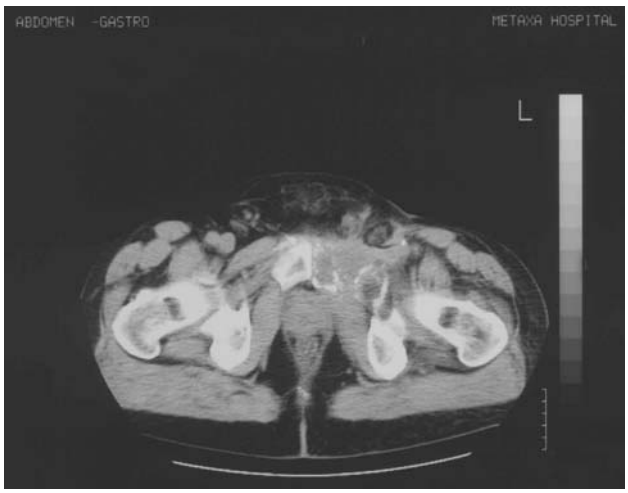

Fig. 1 The metastatic lesion in the left pelvis shown on computer tomography scan

(0.3–4.5 mU/l), severe pain in the area of the pelvis and the left leg, which prevented him from walking and a large pelvic mass measuring 12.5 × 9 cm on computerized tomography (Fig. 1). The mass infiltrated both soft tissues and bone. Fine needle aspiration biopsy of the mass revealed a metastatic neoplasm of thyroid origin. Substitution therapy was stopped. A whole body radioiodine scan was performed with ^{131}I which showed increased uptake of the radioiodine in the area of the left pelvis (Fig. 2). Carbimazole 10 mg was administered twice daily along with propranolol 10 mg twice daily for a month and as soon as euthyroidism was achieved the patient underwent debulking of the pelvic lesion and simultaneous completion thyroidectomy. On histology, the mass proved to be a metastasis with the characters of papillary thyroid carcinoma. The first histology was reviewed and the initial lesion proved to be papillary thyroid carcinoma, follicular variant. Metastatic lesions in other places were not found. The patient was treated by the administration of radioiodine ^{131}I 150 mCi, 200 mCi 2 months later and 200 mCi 5 months later. Thereafter he was given external beam radiotherapy 5500 Gy in the area of the left pelvis 2 months later, 5 months later 150 mCi, and a year later 200 mCi. The total dose received by the patient was 900 mCi radioiodine ^{131}I. Despite the aggressive treatment, thyroglobulin levels 1 year after external radiotherapy were extremely high, being 9,594 ng/ml, antithyroglobulin antibodies 15 IU/ml (normal values < 60 IU/ml), antibodies to thyroid peroxidase 10 IU/ml (normal values < 60 IU/ml), TSH 0.01 mU/l (normal values 0.3–4.5 mU/l), and FT_4 19.2 pmol/l (normal values 9.1–23.8 pmol/l). At that time treatment with the tyrosine kinase inhibitor, sunitinib was initiated. Sunitinib 50 mg daily orally was administered for four consecutive weeks, followed by a 2-week rest period (schedule 4/2, for a complete cycle of 6 weeks). After the administration of sunitinib thyroglobulin levels decreased rapidly to 6,816 ng/ml after 1 month, TSH and FT_4 levels being at that time 0.03 mU/l and 20.0 pmol/l, respectively, decreasing further to 4,506 ng/ml after 3 months, TSH and FT_4 levels being 0.12 mU/l and 21.4 pmol/l, respectively, and to 2,776 ng/ml after 6 months, TSH and FT_4 levels being 4.43 mU/l and 13.5 pmol/l, respectively (Fig. 3). The lesion in the pelvis decreased in size, measuring on CT scan evaluation 5 × 3 cm after 6 months therapy. The patient is now able to walk painlessly and independently without the use of a cane. Sunitinib has been administered to the patient for 15 months. The patient was compliant. He developed only mild stomatitis after the administration of the drug which was easily bearable by the patient, developed on day +18 of every cycle and regressed after discontinuation of the drug, with complete remission after the 2-week rest period. Cell blood count and liver function tests were

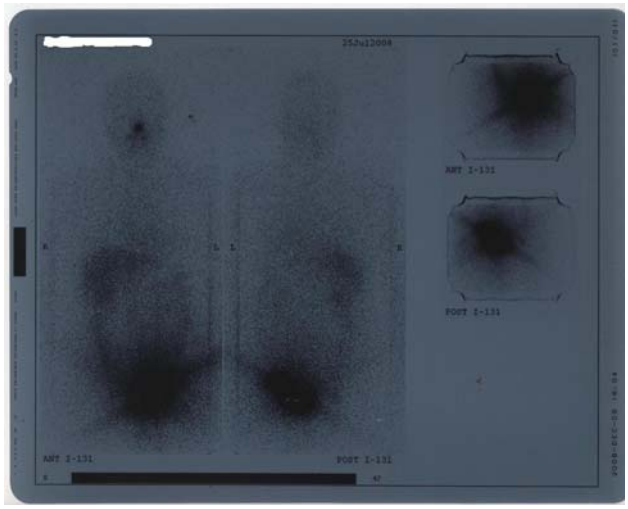

Fig. 2 Visualization in an anterior and posterior view of the papillary thyroid carcinoma metastatic lesion in the pelvis using an ^{131}I whole body scan

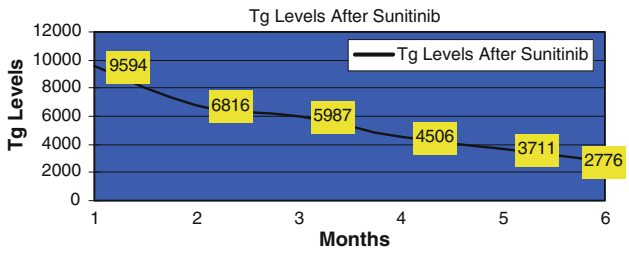

Fig. 3 The response of thyroglobulin (Tg) levels (ng/ml) after the administration of sunitinib in a patient with metastatic papillary thyroid carcinoma over a 6-month period

regularly monitored. No changes in cell blood count or liver function tests were observed which could be attributed to therapy.

Discussion

The case of a patient with metastatic papillary thyroid carcinoma is presented who responded to the administration of sunitinib, an oral tyrosine kinase inhibitor. The relevant literature is reviewed, specifically related to the administration of tyrosine kinase inhibitors in metastatic differentiated thyroid carcinoma.

Activation of tyrosine kinase receptors has been implicated in thyroid cancer [7, 10, 11]. Tyrosine kinase receptors are high-affinity receptors for many polypeptide growth factors, cytokines and hormones, having been shown to be key regulators of normal cellular processes and also to have a critical role in the development and progression of many types of cancer [16, 17]. Tyrosine kinases are enzymes that transfer phosphate groups from ATP to the hydroxyl group of tyrosine residues on signal transduction molecules. Phosphorylation of signal transduction molecules is a major activating event that leads to dramatic changes in tumor growth [18]. Papillary thyroid cancers are associated with mutually exclusive mutations of genes encoding effectors in the mitogen-activated protein kinase pathway including the tyrosine kinase receptors RET, BRAF, and RAS [19]. BRAF and RAS mutations are highly prevalent and mutually exclusive with RET in papillary thyroid cancer, BRAF mutations being the most common genetic change in this type of cancer. Constitutive mitogen-activated protein kinase activation is considered by many investigators to be a key event in papillary thyroid cancer development and progression, making blockade of this pathway a rational therapeutic approach [12, 20, 21]. Chromosomal rearrangements linking the promoter and N-terminal domains of unrelated genes to the C-terminal fragment of the RET protooncogene result in the ectopic expression of chimeric constitutively active forms of the tyrosine kinase, the RET/PTCs, in thyroid cancer [22]. High expression levels of tyrosine kinase receptors for fibroblast growth factor, epidermal growth factor, and vascular endothelial growth factor have also been observed in thyroid cancer [23]. Vascular endothelial growth factor, which is known to promote angiogenesis, is thought to play a critical role in tumor growth [24]. Therefore, the inhibition of tyrosine kinase appears a rational target when aiming at stopping the activity of the disease. In the case described the administration of the multi-targeted tyrosine kinase inhibitor, sunitinib appeared to have a beneficial effect on advanced metastatic papillary thyroid carcinoma.

In the last few years, several clinical trials using tyrosine kinase inhibitors for the treatment of progressive thyroid cancer have been initiated [25–27]. Sunitinib, SU11248, is a derivative of indolinone and has a wide spectrum of inhibitory actions on tyrosine kinases [28]. Sunitinib and related compounds were developed as inhibitors of ATP-binding site of tyrosine kinases and have entered preclinical and clinical trials [29]. Administered orally, sunitinib is a small organic molecule with potent antitumor and anti-angiogenic activity that acts through selectively targeting platelet-derived growth factor receptor, vascular endothelial growth factor receptor, fms-related tyrosine kinase 3 and KIT kinase [30]. By inhibiting the activity of these tyrosine kinase receptors, sunitinib directly targets tumor cell proliferation and survival in cancers in which these receptors are involved. It was rationally designed and chosen for its high bioavailability and its nanomolar range potency against the angiogenic receptor tyrosine kinases, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor. Sunitinib is also a potent inhibitor of RET/PTC oncoproteins, blocking the transforming capacity of RET/PTC [13]. Sunitinib may act both by inhibiting tyrosine kinases in the tumor and tyrosine kinases in the endothelium of vessels that provide blood to the tumor. Therefore, sunitinib may have a beneficial effect on metastatic papillary thyroid carcinoma. In the case described sunitinib induced a partial therapeutic response on metastatic progressive papillary thyroid carcinoma.

Sunitinib demonstrated robust antitumor activity in preclinical studies resulting not only in tumor growth inhibition, but also tumor regression in models of colon cancer, non-small-cell lung cancer, melanoma, renal carcinoma, and squamous cell carcinoma, which were associated with inhibition of VEGFR and PDGFR phosphorylation [31]. Clinical activity was demonstrated in neuroendocrine, colon, and breast cancers in phase-II studies, whereas definitive efficacy has been demonstrated in advanced renal cell carcinoma [14] and in imatinib-refractory gastrointestinal stromal cell tumors [15], leading to US Food and Drug Administration approval of sunitinib for treatment of these two diseases.

The administration of sunitinib has been shown to cause hypothyroidism [32–34]. The mechanism of sunitinib induced hypothyroidism is unknown, possibly related to destructive thyroiditis induced by the drug [35, 36]. Amazingly, in two cases thyroid tissue was impossible to be visualized by thyroid ultrasonography after sunitinib [33]. Recently, sunitinib was found to inhibit thyroid peroxidase activity [37].

The response of a tumor to the administration of therapeutic agents is currently rated by the RECIST criteria [38]. In the case described the sustained decrease in thyroglobulin levels after the administration of sunitinib along with the decrease in the metastatic tumor size and the

clinical improvement of the patient suggest partial response of the disease to the therapeutic agent. Sunitinib was administered to two patients with progressive metastatic thyroid carcinoma, one with papillary and the other with follicular thyroid carcinoma [39]. Both the patients demonstrated sustained clinical response to sunitinib over a duration of 4 years. Positron emission tomography with ^{18}F-fluorodeoxyglucose was performed in both the patients at baseline and 4 weeks after the commencement of sunitinib. In the patient with papillary thyroid carcinoma positron emission tomography showed a partial metabolic response, whereas in the patient with follicular thyroid carcinoma it showed stable disease. In the metastatic papillary thyroid carcinoma inhibition of the RET kinase pathway was demonstrated by immunohistochemistry and Western blot analysis after sunitinib. In a phase-II study, sunitinib was administered to thyroid cancer patients refractory to curative treatment [40]. In 31 differentiated thyroid carcinoma patients evaluable after 2 cycles of sunitinib, a partial response was observed in 13% and disease stabilization in 68%. In 6 medullary thyroid carcinoma patients, disease stabilization was observed in 83%. In another phase-II study, sunitinib was administered to 17 patients with thyroid carcinoma, including 8 with papillary and 4 with medullary [41]. In 15 patients evaluable for response, 1 had a partial response and 12 had stable disease. A partial response to sunitinib was observed in two patients, one with metastatic [42] and the second with locally advanced unresectable medullary thyroid carcinoma [43]. In the first patient, reduction in the size and number of pulmonary metastases and reduction in the size of a palpable cervical lymph node was observed; and in the second, tumor reduction and reduction in the size of a cervical lymph node was observed, serum calcitonin levels decreasing in both. The administration of sunitinib has been shown to have relatively few side effects. Fatigue, diarrhea, hand foot syndrome, neutropenia, and hypertension have been observed [40]. In the patient described sunitinib was shown to be related to the emergence of very few side effects, such as stomatitis, which remitted with continuing administration of the drug. Synergistic effects are seen in vitro when tyrosine kinase inhibitors are combined with radiotherapy and/or conventional chemotherapeutic agents [44]. In the case described, sunitinib may have acted on its own or synergistically with therapeutic radioiodine, as a long-term effect of radioiodine has been observed, and conventional radiotherapy and had a beneficial effect on a patient with progressive metastatic papillary thyroid carcinoma.

In conclusion, the case of a patient with metastatic papillary thyroid carcinoma is described, who responded with partial disease remission to the administration of sunitinib, a novel multiple kinase inhibitor.

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