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Long-term efficacy and safety of fourth-line multikinase inhibitor treatment with lenvatinib in a young papillary thyroid carcinoma patient

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Abstract

Lenvatinib, a multikinase inhibitor, is approved for the treatment of patients with radioiodine-refractory metastatic thyroid cancer on the basis of a Phase III, prospective, double-blind, randomized, placebo-controlled trial that showed longer progression-free survival in the drug-treated arm. Here, we report the case of a young papillary thyroid cancer patient, pretreated with three other kinase inhibitors, who achieved a long-term clinical benefit from lenvatinib in the fourth-line setting.

Keywords: lenvatinib, papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, RAI refractory, sorafenib, sunitinib.

Abbreviations: CT, computed tomography; DTC, differentiated thyroid cancer; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine ablation; TKI, tyrosine kinase inhibitor

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Introduction

Papillary thyroid carcinoma accounts for approximately 85% of thyroid cancers. Most papillary thyroid carcinomas do not progress and are clinically indolent, with a 10-year disease-specific mortality that for differentiated thyroid carcinoma is less than 5%. In these cases, lobectomy or total thyroidectomy, sometimes followed by radioiodine ablation, is the treatment of choice. Systemic therapies are reserved for patients with metastatic, radioiodine-refractory, progressing, symptomatic disease [1]. Besides palliative radiotherapy, low-dose chemotherapy or local therapies, treatment options for these patients include sorafenib or lenvatinib, two multikinase inhibitors approved by the Food and Drug Administration on the basis of a Phase III, prospective, double-blind, randomized, placebo-controlled trial that showed longer progression-free survival in the drug-treated arms. Both drugs are thought to be angiogenesis suppressors because, over their action against other kinases, they inhibit VEGF receptors 1, 2, and 3 [1]. Although the two drugs have not been compared formally, lenvatinib appears to be more effective than sorafenib [2]. Here, we present the case of a young man suffering from a poorly differentiated thyroid cancer, derived from a papillary thyroid carcinoma of the follicular variant, previously treated with sorafenib, sunitinib, and pazopanib, who achieved clinical benefit, progression-free survival, and bone metastases regression with lenvatinib.

Case report

In April 2011, a 42-year-old patient underwent total thyroidectomy because of a Thy 3 cytology report on a left lobe thyroid nodule fine needle aspiration biopsy. The nodule involved the entire left thyroid lobe and, on histologic examination, resulted to be a poorly differentiated thyroid cancer, arisen on a papillary thyroid carcinoma of the follicular variant. The cancer had capsular and vascular invasion, with a high mitotic index (5 mitosis × 10 high power fields) and high Ki67 expression (15%). In June 2011, both a positron emission tomography (PET) scan and a high-resolution thorax computed tomography (CT) scan resulted negative. In September 2011, the patient underwent radioiodine ablation, with the administration of 3700 MBq of 131I. The post-treatment whole-body scan showed only thyroid bed uptake. In December 2011, during the first follow-up visit after radioiodine treatment, because of high basal thyroglobulin levels (89.35 ng/mL; TSH 0.130 mcU/mL), total body CT, and PET scans were repeated. Both revealed the new appearance of vertebral osteolytic lesions, confirmed also by magnetic resonance imaging (MRI), in the body of D10 and L1 (of 13 and 6 mm,

respectively). PET scan also showed uptake on the eighth and ninth right ribs. In January–February 2012, the patient underwent analgesic radiation on the thoracolumbar spine (D9-L2; 30 Gy).

In March 2012, bone progression was confirmed and treatment with sorafenib (400 mg twice daily) was started. Moreover, treatment with zoledronic acid (4 mg once monthly) was started, based on favorable experience in bone metastases management [3]. In June 2012, due to back pain, another cycle of radiation therapy was performed on cervical and thoracic spine (C4 and D6-D7; 20 Gy). During treatment with sorafenib, the patient experienced grade 2 hair loss, hand-and-foot syndrome, mucosites, and diarrhea, which induced a dose reduction in July 2012 (200 mg, twice daily).

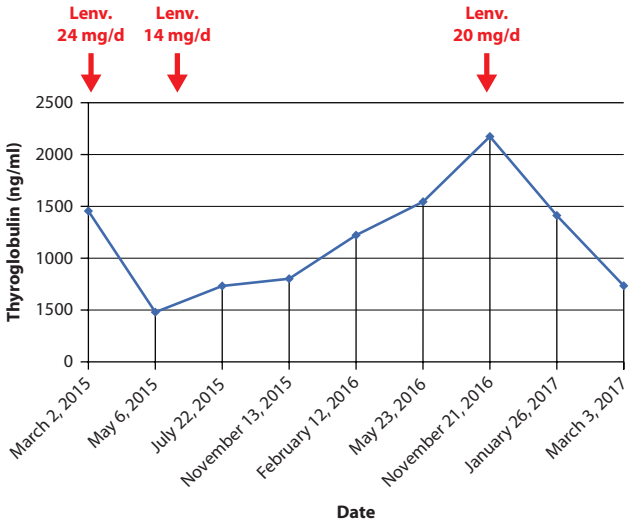
Sorafenib allowed bone lesion stabilization until February 2013, when a brain MRI and a PET scan showed progression of the spine lesions and the appearance of a left frontal skullcap metastasis. Thus, sorafenib treatment was discontinued and sunitinib 37.5 mg/day, 20 days on and 10 days off, was started. During sunitinib treatment, the patient developed grade 2 anemia.

After 11 months of sunitinib treatment, which initially allowed volume reduction of the skull lesion (from 13 × 12 mm in February 2013 to 13 × 6.8 mm in June 2013), new frontal bone disease progression was assessed, and in February 2014, the patient underwent neurosurgery for the removal of the skull metastases.

In April 2014, a PET scan showed bone progression at the sternum, ribs, costovertebral joints, vertebral column, and at pelvic bone level. Thus, in May 2014, sunitinib was discontinued and pazopanib 800 mg daily started as third-line tyrosine kinase inhibitor (TKI). This line of treatment was not very efficacious, and during pazopanib treatment, the patient experienced gradual bone disease progression needing spine analgesic radiation twice (June 2014, D7-D8 and L1, 30 Gy; and October 2014, L3-S1, 30 Gy). In December 2014, zoledronic acid was stopped and denosumab 120 mg s.c. once monthly was started. During treatment with pazopanib, he experienced grade 2 anemia and a progressive increase in gamma-glutamyl peptidase which ultimately required a dose reduction to 400 mg/day.

In March 2015, due to biochemical (thyroglobulin levels of 1447 ng/mL) and imaging progression of disease, he started lenvatinib 24 mg daily, as fourth-line treatment. After 2 months of lenvatinib treatment, in May 2015, thyroglobulin levels dropped to 477.6 ng/mL (Figure 1), and both PET and CT scans showed a significant reduction of bone lesion volume (Figure 2). However, the full 24 mg daily dose was not well tolerated and, after 4 months, due to extreme fatigue (grade 3) and the recurrence of hypertensive crises (grades 3 and 4), the dose was reduced, initially to 20 and then to 14 mg daily. He continued the 14 mg daily dose from June 2015 until December 2016. The regimen was well tolerated without any significant adverse event and with a good quality of life. However, in this period of time, he presented a progressive increase of thyroglobulin (November 2015, 804 ng/mL; May 2016, 1539 ng/mL, November 2016, 2174 ng/mL) (Figure 1). Moreover, an increase in standardized uptake values at sternum, ribs, vertebral column, and left jaw metastases could be detected in the December 2016 PET scan (Figure 2). Conversely, at CT scan, the volume of all bone lesions continued to be stable and significantly small, compared to the March 2015 evaluation (Figure 2). Nevertheless, lenvatinib was increased from 14 to 20 mg/daily. After 3 months, in March 2017, thyroglobulin levels were significantly reduced (728 ng/mL) and fluorodeoxyglucose (FDG) uptake was stable in almost all the bone lesions at PET scan. Interestingly, with the dose increase, the patient has only experienced few low-grade side effects such as easily manageable grade 2 weight loss, grade 2 increase in blood pressure, well controlled by a strengthening of the antihypertensive drug therapy, and increase of serum creatinine up to 1.9 mg/dL, which promptly receded with a 5-day lenvatinib interruption and a more accurate management of blood pressure drugs.

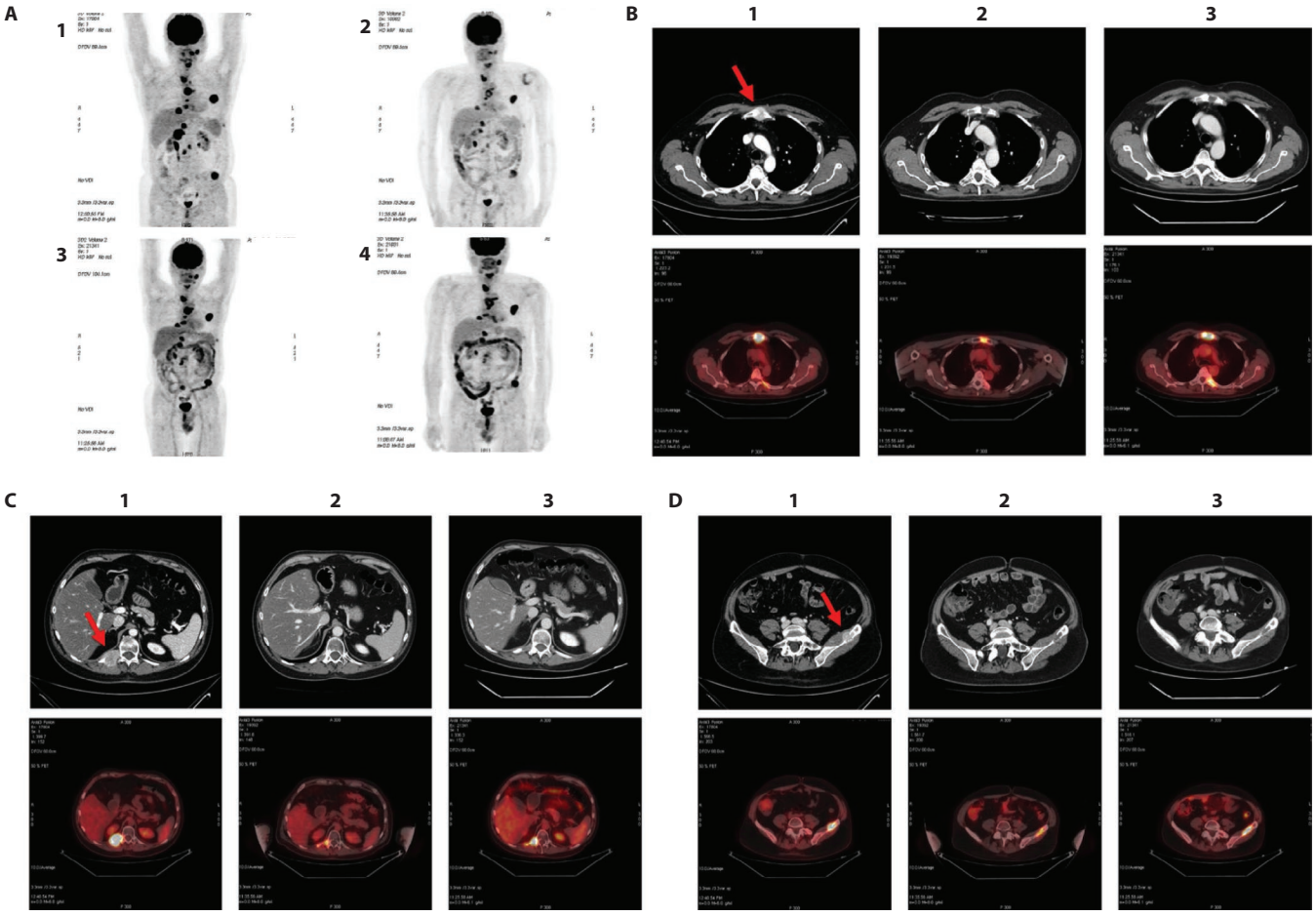
Figure 1. Changes in thyroglobulin levels during lenvatinib treatment.



Discussion

This case report raises many interesting issues. First of all is the timing to start kinase inhibitor therapy. According to the 2015 American Thyroid Association guidelines (recommendation 96), kinase inhibitor therapy should be considered in radioactive iodine ablation (RAI)-refractory differentiated thyroid cancer (DTC) patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches (e.g., surgery, radiation therapy, thermal ablation) [4]. Moreover, DTC patients who experience disease progression while on initial kinase inhibitor therapy without prohibitive adverse effects should be considered

Figure 2. **Volume and functional activity of the most significant metastasis during lenvatinib treatment. (A) Total body PET scans. 1) March 2015; 2) November 2015; 3) December 2016; 4) March 2017. (B) Sternum metastasis. Upper panels CT scans. Lower panels PET/CT scans. 1) March 2015; 2) November 2015; 3) December 2016. (C) Costo-vertebral metastasis involving the 11th right rib. Upper panels CT scans. Lower panels PET/CT scans. 1) March 2015; 2) November 2015; 3) December 2016. (D) Iliac wing metastasis. Upper panels CT scans. Lower panels PET/CT scans. 1) March 2015; 2) November 2015; 3) December 2016.**



candidates for second-line kinase inhibitor therapy (recommendation 97) [5]. Our patient fulfilled both the recommendations, although we pushed further and prescribed third- and fourth-line treatments. This is an emblematic case because, to our knowledge, we report for the first time a fourth-line multikinase inhibitor treatment in thyroid cancer.

Another point of discussion is the toxicity of these drugs. Kinase inhibitors are associated with numerous adverse effects including diarrhea, fatigue, hypertension, hepatotoxicity, skin changes, nausea, increased levothyroxine dosage requirement, changes in taste, weight loss, thrombosis, bleeding, heart failure, hepatotoxicity, gastrointestinal tract fistula formation, and intestinal perforation [6]. As a consequence, great care must be taken not only in selecting appropriate patients for therapy, but also in monitoring patients who receive kinase inhibitor therapy and in introducing the appropriate countermeasures when necessary [7]. These potential side effects, as underlined in the guidelines, have high probability to impact negatively on the quality of life, resulting in dosage reductions in nearly two-thirds of treated patients or treatment discontinuation in up to 20% of patients. The risk of therapy-related death in cancer patients treated with oral kinase inhibitors is about 1.5 to 2%. Lenvatinib was associated with severe toxicities in 75% of patients and therapy-attributed mortality in 2.3% of patients. However, compared to placebo, lenvatinib treatment was associated with a prolongation of median progression-free survival of 14.7 months, with a RECIST response rate of 65%, including some complete responses [8,9]. Our patient showed an initial outstanding response with lenvatinib 24mg/day for 4 months, followed by a disease stabilization when lenvatinib dosage was reduced to 14 mg/day due to the development of grade 3 to 4 side effects. Interestingly, a new increase of the drug dose to 20 mg was associated with few low-grade easily manageable side effects.

Another critical question often faced in kinase inhibitor-treated patients is when treatment should be discontinued once initiated. American Thyroid Association (ATA) guidelines recommend that therapy should be continued so long as

net benefit exceeds net detriment [4]. In case of slow RECIST disease progression after significant tumor response, treatment may be maintained so long as overall disease control is maintained, providing that toxicities are manageable; when global progression is rapid, therapy should be discontinued. In case of focal/oligometastatic disease progression, loco-regional therapies can be practiced, maintaining systemic therapy. In our case, since the patient has been responding so well to the treatment, with manageable side effects, we are not considering treatment discontinuation. However, according to guidelines, we will not discontinue therapy neither in the case of the evidence of slow progression nor in the case of focal/oligometastatic progression. In the latter case, we will refer him for loco-regional treatments.

Another remarkable issue is the use of bisphosphonate or denosumab therapy in patients with diffuse and/or symptomatic bone metastases from RAI-refractory DTC, either alone or concomitantly with other systemic therapies, even if kinase inhibitor therapy is intended or ongoing (recommendation 101 of ATA Guidelines) [4]. In detail, a beneficial effect of bisphosphonates on differentiated thyroid carcinoma bone metastases in reducing or delaying the appearance of skeletal-related events, including bone fractures, spinal cord compression, and hypercalcemia, has been described [3]. Some authors believe that this association might increase the risk of osteonecrosis of the jaw. Our patient followed these regimens without specific side effects and probably experiencing a significant clinical benefit. Thus, this report highlights the feasibility of the treatment with bisphosphonate or denosumab in patients with bone metastasis who are concomitantly treated with TKIs.

Finally, a last important issue is represented by the changes of lenvatinib dosage during treatment. Although patients frequently need a reduction in drug dosage due to the development of toxicities, in clinical practice lenvatinib rechallenges after treatment interruption or dose increments have been advocated for patients with progressive disease, as they have been shown to be beneficial. In detail, our patient, after an initial response to a 24 mg per day regimen, reduced lenvatinib to 14 mg per day, experiencing a volumetric stabilization of the disease still persisting. However, thyroglobulin and cancer tissue uptake of 18-FDG showed progression under this condition. These data led us to increase lenvatinib dosage to 20 mg per day. Interestingly, this action was associated with a significant drop in thyroglobulin. Thus, we expect a possible prolongation of the time of progression-free survival.

Conclusion

This case report is emblematic, because it describes an excellent response to lenvatinib in a fourth-line treatment setting. To our knowledge, it is the first report in the literature of a successful use of a fourth-line multikinase inhibitor for thyroid cancer. Although there is no clear evidence that TKIs are able to prolong patient's overall survival, we believe that 5 years of TKIs treatment have certainly inhibited/slowed down disease progression and allowed in this rapidly progressing poorly differentiated thyroid carcinoma patient a significant gain in survival and quality of life. Among the four tested drugs, lenvatinib was by far the most effective.

Future perspective

Recent discoveries in molecular medicine have led to major advances in the treatment of patients with thyroid cancer. The future development of more effective therapies with greater specificity for oncogenic targets and combinatorial regimens could probably allow to overcome resistance to single agents [1]. In the future, other treatment modalities, such as radioiodine resensitization therapy, immunotherapy, or drugs directed to other targets (e.g., BRAF kinase inhibitors, inhibitors of MEK kinase), may also offer additional therapeutic options. Patients could also be enrolled in "basket trials," in which the efficacy of a drug targeting a particular mutation is studied in different types of cancers [1]. However, the use of these novel approaches ahead of VEGFR-directed kinase inhibitors is not yet indicated unless within the context of therapeutic clinical trials, or alternatively when used as "salvage" therapies after disease progression has occurred despite prior VEGFR-directed kinase inhibitor therapy.

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