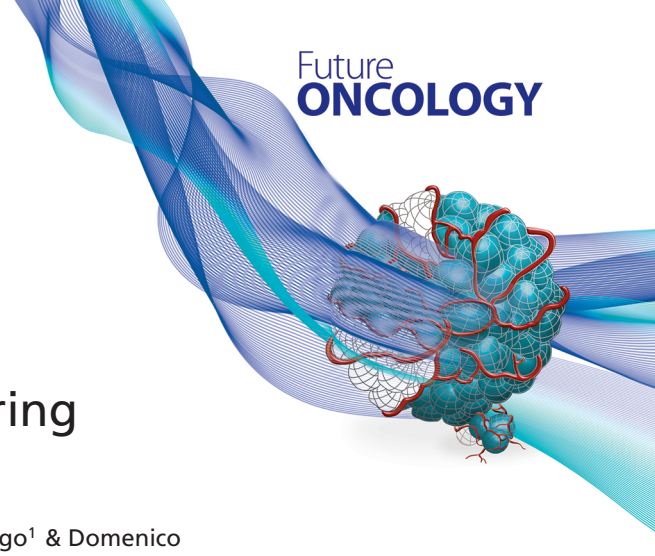
Supplement

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY



Management of one patient with oligoprogressive thyroid cancer during treatment with lenvatinib

Tommaso Porcelli*[,1], Francesca Sessa[1], Carla Gambale[1], Cristina Luongo[1] & Domenico Salvatore[2]

[1]Department of Clinical Medicine & Surgery, University of Naples "Federico II", Naples, Italy

[2]Department of Public Health, University of Naples "Federico II", Naples, Italy

*Author for correspondence: Tel.: +39 339 763 9462; tommasoporcelli@gmail.com

Recent thyroid cancer guidelines found it reasonable to use local therapies during treatment with tyrosine kinase inhibitors (TKIs) in selected patients with oligoprogressive disease, namely, in the presence of a single progressing lesion in an otherwise TKI-responsive metastatic cancer. However, there is a lack of experience in the management of oligoprogressive thyroid cancers. This report illustrates the case of one patient with oligoprogressive thyroid cancer during therapy with lenvatinib. We found that the application of local ablative therapy in oligoprogressive disease prolonged the progression-free survival and thus extended the time to therapy interruption. However, the optimal care for TKI-treated oligoprogressive cancers remains unclear and needs to be investigated in prospective trials.

First draft submitted: 25 February 2019; Accepted for publication: 23 July 2019; Published online: 14 August 2019

Keywords: advanced thyroid cancer • lenvatinib • local ablative therapy • oligoprogression • radiotherapy • tyrosine kinase inhibitors

Progressive and/or symptomatic advanced thyroid cancers not amenable to local control of the disease benefit from systemic therapy with tyrosine kinase inhibitors (TKIs), namely, anticancer agents that determine a cytostatic effect by selectively targeting critical oncogenic pathways [1,2]. Although they provide a significant improvement in progression-free survival (PFS), TKIs do not eradicate the cancer [3]. In fact, the cancer inevitably progresses often after 1–2 years of treatment [4]. This progression mainly occurs through novel genetic alterations that overcome the TKI cytostatic action [5]. Unlike cytotoxic chemotherapy, during which treatment failure generally means global disease progression and need for treatment change, TKI resistance may lead to several patterns of progression [6]. Notably, the oligoprogressive disease (OPD), which means the progression limited to one or a few sites of disease in an otherwise treatment-responsive cancer, can be managed without discontinuing the ongoing therapy [7,8]. Here, we report the case of one patient with oligoprogressive thyroid cancer on therapy with lenvatinib, who continued the systemic therapy thanks to the concomitant use of directed therapies of the isolated progressing lesions.

Case presentation

A 54-year-old woman presented to our Institute due to progressive advanced thyroid cancer with symptomatic bone metastases. She had undergone total thyroidectomy in February 2012 for the removal of a Hürthle cell carcinoma with a maximum diameter of 4.5 cm, extensive vascular invasion and focal extrathyroidal extension. Even though there was a high risk of structural disease recurrence, the patient refused radioactive ^{131}I (RAI) ablation and dropped out of follow-up. After almost 3 years, she decided to undergo further medical treatments and a dose of 110 mCi of RAI was administered. Stimulated serum thyroglobulin (Tg) was 206 ng/ml and postablation whole-body scan revealed uptake in multiple neck sites and in the vertebra T8. After 7 months, the patient received a second course of RAI at a dose of 208 mCi, after which stimulated Tg was 304 ng/dl and postablation whole-body scan showed an unchanged iodine uptake. Nevertheless, the total-body CT scan revealed the presence of several iodine-refractory bone metastases, specifically, at vertebrae T1, T5 and in the right femur neck. After a few months, the patient started to complain of back pain. A PET/CT scan revealed a global increase in the dimension of metastases, with

Future Medicine

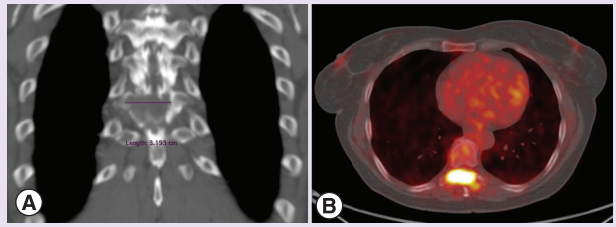


Figure 1. Metastasis at vertebra T8 prior to the treatment with lenvatinib. (A) CT scan of dorsal spine in coronal view. **(B)** A concomitant PET scan (axial view) showed intense ^{18}FDG uptake in T8.

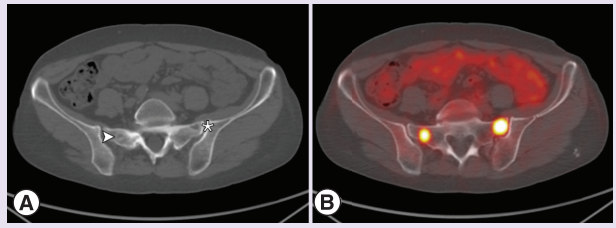


Figure 2. New lesion in right sacrum appeared after 16 months of therapy with lenvatinib. (A) CT and **(B)** PET scan of the new metastasis appeared in right sacrum (arrow) at december 2017. The lesion in left sacrum (star) was present before lenvatinib start.

the greatest lesion located at vertebra T8 (Figure 1), and the appearance of new lesions in L1 and the left sacrum. Therefore, in August 2016, the patient was subjected to 3D-conformal radiotherapy (3D-CRT) at T8 and the right femur neck, with a dose of 20 Gy in five fractions, respectively. Then, she received systemic therapy with lenvatinib at a daily dose of 24 mg and denosumab 120 mg every 4 weeks. Before the administration of lenvatinib, basal serum Tg was 1170 ng/ml, with negative serum anti-Tg antibodies, and the sum of diameters of five target lesions was 75 mm. Lenvatinib was reduced to 20 mg daily after 17 weeks of therapy due to grade 2 weight loss, and to 14 mg daily after other 4 weeks due to the persistency of weight loss and diarrhea. The best treatment response was reached after 6 months, when the target lesion sum reduced to 68 mm and basal serum Tg was 354 ng/ml. Lenvatinib produced stable disease until December 2017, when a new lesion appeared in the right sacrum, with a maximum diameter of 6 mm (Figure 2), along with a slow increase in global tumor volume, that reached 77 mm in the sum of target lesions. The new metastasis was clinically silent and did not worsen the pain control, therefore lenvatinib was not discontinued. However, in April 2018, the lesion in T5 had progressed and become a high risk for vertebral fracture (Figure 3). Given the good pain control and the substantial stability of the other metastases, including the new right sacral lesion, lenvatinib was continued and 3D-CRT was applied to T5 at a total dose of 30 Gy. Cement injection was not feasible due to posterior edge involvement and was therefore not provided. The patient suspended lenvatinib during the time of radiotherapy (RT), which was delivered in ten daily fractions. At a subsequent CT scan in October 2018, the RT-treated lesion in T5 was stable. Nevertheless, the metastasis in the right sacrum enlarged and the patient complained of lower back pain. Hence, in November 2018, 8 Gy in a single dose of 3D-CRT was delivered to the sacrum lesion, thereby achieving a relief of symptoms. Both the RT treatments were well tolerated, and no side effects occurred. At the last CT scan, performed in January 2019, the RT-treated lesions were unchanged, and the remaining tumor bulk was still responsive to treatment (sum of target lesions = 84 mm). Therefore, lenvatinib treatment is currently ongoing.

Discussion

The assessment of treatment failure and the decision for drug interruption are critical issues in patients undergoing therapy with TKIs. In clinical trials, the loss of drug efficacy generally equals to the assessment of disease progression according to the RECIST criteria [9]. Conversely, in the daily oncological practice, several conditions that fall within

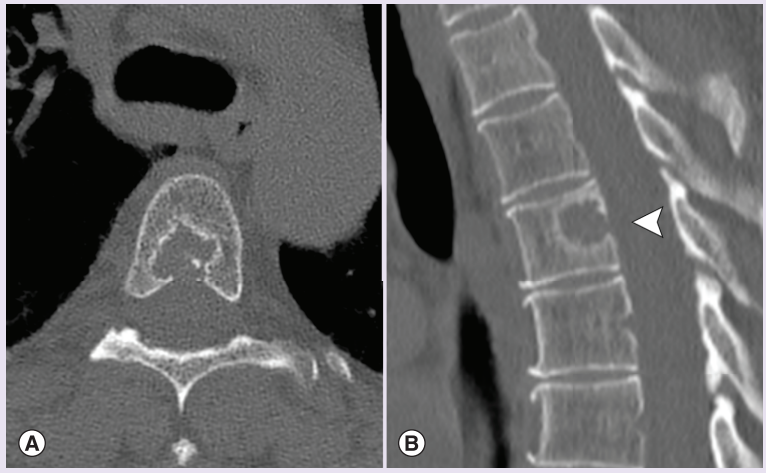


Figure 3. Progressing lesion in vertebra T5 after 20 months of lenvatinib treatment. CT scan of the progressing lesion in vertebra T5 from **(A)** axial and **(B)** sagittal view.

the definition of progressive disease do not correspond to a therapeutic failure and, therefore, may be managed without therapy interruption [10,11]. Among these, the OPD can be controlled by local treatment of the single progressive lesions [12]. This approach allows the prosecution of the ongoing systemic therapy and thus being beneficial for preventing overall thyroid cancer progression, for which systemic treatment options are limited [13]. In fact, advanced thyroid cancers poorly respond to cytotoxic chemotherapy and, outside clinical trials, the only agents approved for radioiodine-refractory follicular cell-derived cancers are the multitarget TKIs sorafenib and lenvatinib [14]. Therefore, it is important to maximize the duration and efficacy of each single line of therapy.

In our patient, the occurrence of RECIST progression has not been followed by the interruption of lenvatinib. The criteria for disease progression [9] were met 16 months following initiation of therapy upon the appearance of a new bone metastasis, specifically, in the right sacrum. Nevertheless, we felt that it would be in the patient's best interest to continue with lenvatinib therapy, because the benefits from the persistent control on tumor bulk largely outweighed the risks from this new lesion. At that time, the systemic therapy was continued without additional treatments, since the new lesion was clinically silent and at a low-risk location. Conversely, we associated a local ablative therapy (LAT) to the systemic treatment when the tumor manifested a clinically relevant OPD. As previously shown, the progressing lesion in vertebra T5 was related to a significant fractural risk, and the growing right sacral metastasis caused bone pain. In both cases, the administration of 3D-CRT was able to arrest the progression of the lesions and allowed to extend the PFS.

The choice of which specific LAT to use in OPD is highly dependent on the location and the size of the progressing lesions [15,16]. The metastasis at T5 was unsuitable to cement vertebroplasty and was therefore treated with a fractioned regimen of 3D-CRT. Furthermore, the symptomatic sacral metastasis was smaller in dimensions but painful, thus a palliative treatment at a single-dose irradiation was delivered. As demonstrated in this case report, the LAT of single TKI-resistant lesions offers the advantage to not waste the persistent cytostatic effect of an ongoing TKI, that in OPD continues to act on the bulk of tumor volume [17]. Moreover, LATs are generally well tolerated and clear of negative consequences in terms of new side effects that are often related to the switch to a subsequent line of systemic therapy [18].

Conclusion

This report shows that TKI-treated oligoprogressive thyroid cancer may be managed with the use of LAT, without discontinuing the ongoing systemic therapy. In our patient, the application of LAT prolonged the PFS and thus extended the time to treatment change.

10.2217/fon-2019-0110

Future perspective

To date, TKIs are the only systemic agents with a significant impact on PFS of patients with advanced metastatic thyroid cancer [19]. Therefore, it is important to take maximum advantage from each line of TKI therapy. However, the optimal care for TKI-treated oligoprogressive cancer patients is still unclear and prospective trials are needed to assess the benefits in terms of overall survival deriving from such an approach.

Executive summary

- Progressive and/or symptomatic advanced thyroid cancers not amenable to local control of the disease benefit from systemic therapy with tyrosine kinase inhibitors (TKIs).
- Although they provide a significant improvement in progression-free survival, TKIs do not eradicate the cancer.
- TKI resistance may lead to several patterns of progression. One pattern is the oligoprogressive disease (OPD), which means the progression limited to one or a few sites of disease in an otherwise treatment-responsive cancer.
- OPD can be managed without discontinuing the ongoing therapy.
- A 54-year-old woman presented at our Institute due to progressive advanced thyroid cancer with symptomatic bone metastases.
- She had OPD during therapy with lenvatinib.
- Treatment was continued and the application of local ablative therapy prolonged the progression-free survival and thus extended the time to therapy interruption.

Disclaimer

The supporting company was not offered the opportunity to revise the paper and had no role in the decision to submit.

Financial & competing interests of disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Editorial assistance was provided by A Shah and L Giacomelli (Polistudium srl, Milan, Italy) on behalf of Content Ed Net. This assistance was supported by Eisai.

Informed consent

The authors state that they have obtained verbal and written informed consent from the patient for the inclusion of his medical and treatment history within this case report.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Schlumberger M, Tahara M, Wirth LJ *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* 372(7), 621–630 (2015).

•• **Demonstrates lenvatinib efficacy.**

2. Brose MS, Nutting CM, Jarzab B *et al.* Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, Phase III trial. *Lancet* 384(9940), 319–328 (2014).
3. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. *Nat. Rev. Clin. Oncol.* 11(8), 473–481 (2014).
4. Jiao Q, Bi L, Ren Y *et al.* Advances in studies of tyrosine kinase inhibitors and their acquired resistance. *Mol. Cancer* 17(36), 1–12 (2018).
5. Lim SY, Menzies AM, Rizos H. Mechanisms and strategies to overcome resistance to molecularly targeted therapy for melanoma. *Cancer* 123(S11), 2118–2129 (2017).
6. Morgan RL, Camidge DR. Reviewing RECIST in the era of prolonged and targeted therapy. *J. Thorac. Oncol.* 13(2), 154–164 (2018).
7. Weickhardt AJ, Scheier B, Burke JM *et al.* Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J. Thorac. Oncol.* 7(12), 1807–1814 (2012).

8. Chan OSH, Lee VHF, Mok TSK *et al.* The role of radiotherapy in epidermal growth factor receptor mutation-positive patients with oligoprogression: a matched-cohort analysis. *Clin. Oncol. (R. Coll. Radiol.)* 29(9), 568–575 (2017).

9. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45(2), 228–247 (2009).

• **Relevant for practice.**

10. Gandara DR, Li T, Lara PN Jr *et al.* Acquired resistance to targeted therapies against oncogene-driven non-small-cell lung cancer: approach to subtyping progressive disease and clinical implications. *Clin. Lung Cancer* 15(1), 1–6 (2014).

11. Oxnard GR, Morris MJ, Hodi FS *et al.* When progressive disease does not mean treatment failure: reconsidering the criteria for progression. *J. Natl Cancer Inst.* 104(20), 1534–1541 (2012).

12. Porcelli T, Sessa F, Luongo C *et al.* Local ablative therapy of oligoprogressive TKI-treated thyroid cancer. *J. Endocrinol. Invest.* 42(8), 871–879 (2019).

13. Tumino D, Frasca F, Newbold K. Updates on the management of advanced, metastatic, and radioiodine refractory differentiated thyroid cancer. *Front. Endocrinol. (Lausanne)* 8, 312 (2017).

14. Haugen BR, Alexander EK, Bible KC *et al.* 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 26(1), 1–133 (2016).

•• **For evidence-based practice.**

15. Cazzato RL, Garnon J, Koch G *et al.* Current role of interventional radiology in the management of visceral and bone metastases from thyroid cancer. *Gland Surg.* 7(2), 80–88 (2018).

16. Osborn VW, Lee A, Yamada Y. Stereotactic body radiation therapy for spinal malignancies. *Technol. Cancer Res. Treat.* 17, 1–15 (2018).

17. Rowe SP, Tran PT, Fishman EK *et al.* Oligoprogression: what radiologists need to know about this emerging concept in cancer therapeutic decision-making. *Acad. Radiol.* 24(7), 898–900 (2017).

18. Yuan A, Kurtz SL, Barysauskas CM *et al.* Oral adverse events in cancer patients treated with VEGFR-directed multitargeted tyrosine kinase inhibitors. *Oral Oncol.* 51(11), 1026–1033 (2015).

19. Weitzman SP, Sherman SI. Novel drug treatments of progressive radioiodine refractory differentiated thyroid cancer. *Endcorinol. Metab. Clin. North Am.* 48(1), 253–268 (2019).

10.2217/fon-2019-0110