

**THERAPY OF RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CANCER
– CLINICAL CASE**

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Abstract

Introduction: Surgery is the first method of choice for treatment of patients with differentiated thyroid cancer (DTC). Postoperatively, in some cases radioiodine therapy is considered suitable. In cases of radioiodine-refractory advanced DTC treatment with tyrosine-kinase inhibitors (TKI) is recommended.

Case description: A 79-year-old female, who underwent thyroidectomy for DTC in the past, followed by another surgery for metastases in the right lateral neck compartment, was admitted for assessment regarding data for SPECT-positive formation in the neck. Laboratory testing revealed a biochemical constellation of progression of the disease: TSH – 4,646 mU/L (0,38-5,33), anti-Tg-Ab – 0,1 U/mL (0-4), thyroglobulin – 198,5 ng/ml (5-55) while on suppressive dose of levothyroxine. The ultrasound examination revealed a soft tissue formation in the right thyroid lobe and multiple pathological lymph nodes in the left lateral neck compartment. The cytological analysis of the formation in the right thyroid lobe proved malignancy and the positive wash-out analysis for thyroglobulin (>1000 ng/ml) confirmed recurrence of DTC. Due to reluctance of the patient to undergo another surgery she was referred for radioiodine therapy. Two months later a progression of the serum thyroglobulin was observed - 937,56 ng/ml, which prompted treatment with TKI – Sorafenib. Due to marked adverse reactions, the dose of the medication was reduced to 200mg OD. 4 months later a significant drop in the levels of thyroglobulin was noted (267 ng/ml).

Conclusion: Therapy with TKI in patients with DTC is a promising new method for treatment of patients with radioiodine-refractory disease. Despite the marked adverse side effects, which can occur during the treatment with this type of medications, they have a strong potential for improving the prognosis of patients with advanced DTC.

Keywords: *differentiated thyroid cancer, sequential therapy, radioiodine therapy, tyrosine-kinase inhibitors*

Introduction

Surgery is the first method of choice for treatment of patients with differentiated thyroid cancer (DTC). Postoperatively, in cases of intermediate and high-risk of recurrence of the disease, adjuvant radioiodine therapy is recommended. In cases recurrent disease or radioiodine-refractory advanced DTC, treatment with tyrosine-kinase inhibitors (TKI) is recommended.

Case description

A 79-year-old female, who underwent thyroidectomy for DTC in the past, was admitted for assessment regarding data for SPECT-positive formation in the neck. In 2015 the patient underwent thyroidectomy with a histological result of papillary thyroid cancer and underwent radioiodine therapy. In 2018 another surgery was performed due to recurrence of the disease. There was no data for postoperative radioiodine therapy. In May 2025 the patient was admitted to the clinic of Endocrinology at University Hospital “Kaspela” in Plovdiv, Bulgaria due to recent data showing a SPECT-ST positive formation in the neck. The patient had multiple concomitant diseases: arterial hypertension, congestive heart failure, cerebrovascular disease, type 2 diabetes, iron-deficient anemia. Laboratory testing revealed a biochemical constellation for progression of the disease: TSH

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– 4,646 mU/L (0,38-5,33), anti-Tg-Ab – 0,1 U/mL (0-4), thyroglobulin – 198,5 ng/ml (5-55) while on suppressive dose of levothyroxine – LT4 125mcg – 6 days a week, 100mcg – 1 day a week. The ultrasound examination revealed a soft tissue formation in the right thyroid lodge and multiple pathological lymph nodes in the left lateral neck compartment. The formation in the right thyroid lodge was markedly hypoechoic with irregular shape, blurred margins and a diameter of 17mm (Fig.1 and 2). The cytological analysis of the formation in the right thyroid lodge proved malignancy and the positive wash-out analysis for thyroglobulin (>1000 ng/ml) confirmed recurrence of DTC. The cytological result and wash-out analysis for thyroglobulin from lymph nodes in the left lateral neck compartment were negative (FNA-Tg – 0,77 ng/ml). Due to reluctance of the patient to undergo another surgery she was referred for radioiodine therapy. In the meantime, the dose of levothyroxine was increased – LT4 – 150mcg – 4 days, 125mcg – 3 days. On 18 Sep 2024, the patient underwent radioiodine therapy with 128mCi. In November 2024, a progression of the serum thyroglobulin was observed - 937,56 ng/ml, which prompted treatment with TKI. TSH was 9,31 mU/L, anti-Tg-Ab were negative, the patient admitted to having taking the levothyroxine simultaneously with her other medications. The oncology team started the patient on Sorafenib 800mg/daily. Immediate adverse reactions to the medication were noted. The patient reported palmoplantar erythematous rash and severe diarrhea, resistant to loperamide treatment. Due to the adverse side-effects, the dose was tapered down to 200mg/daily. The patient reported alleviation of the rash, however the gastrointestinal symptoms continued almost unchanged. Due to marked adverse reactions, the dose of the medication was reduced to 200mg OD. On 28 Apr 2025, the patient was admitted for reassessment. A significant drop in the levels of thyroglobulin was noted (267 ng/ml), despite being on a minimal dose of TKI. TSH was 9,236 mU/L, anti-Tg-Ab - 0.0 U/mL. No dynamics regarding the size of the lesions in the neck area was noted. Treatment with prebiotics and administration of carob powder was initiated with a significant beneficial effect on the diarrhea.

Discussion

Differentiated thyroid cancer is the most common type of thyroid malignancy. Usually, it has a favorable prognosis and a low risk of recurrence. In cases of more aggressive histological types, signs of metastasis or nearby tissue invasion, the patient is classified as intermediate or high-risk for recurrence. In such cases, postoperative radioiodine (RAI) therapy is indicated. Radioiodine-refractory DTC is defined as lack of iodine uptake in the metastatic tissue, loss of ability of the tumor to concentrate RAI, partial concentration of RAI in the lesions or disease progression despite significant concentration of RAI [1]. When a patient with DTC is classified as refractory to RAI, there is no indication for further RAI treatment. Therapy of RAI-refractory DTC may be a challenging task regarding balance of quality of life and efficiency of treatment. Two types of tyrosine-kinase inhibitors are available up to this date in Bulgaria for treatment of RAI-refractory DTC – sorafenib and lenvatinib. While lenvatinib demonstrates advantages in progression-free survival (PFS) and objective response rate (ORR), it also has a higher incidence of certain adverse events such as hypertension, kidney and liver dysfunction [2]. Bearing this in mind, in the current case of an elderly polymorbid patient, the option of sorafenib was chosen. Well-known side effects of sorafenib are the hand-foot syndrome and diarrhea. Despite local treatment of the skin lesions and anti-diarrheal treatment, these adverse reactions can sometimes be very persistent and alarming to the patients, leading to a decrease in quality of life.

Sorafenib is a TKI, used not only for treatment of advanced DTC, but for hepatocellular carcinoma as well. A possible link between the severity of TKI toxicities and the positive effect on the primary tumor has been discussed, such as better time to progression and improved overall survival [3]. This is also evident in the presented case, in which despite the administration of a suboptimal dose of Sorafenib, serious adverse reactions were noted alongside with a dramatic improvement in thyroglobulin levels over a short period of time.

Treatment of toxicities due to TKI remains a hot topic. Usually tapering down the dose leads to alleviation of the symptoms, however this might not always be beneficial. It is important to warn the

patient for possible side effects before the treatment starts. In our case of refractory diarrhea, despite lowering the dose of the medication and the use of loperamide, there was minimal effect. Interestingly, the introduction of probiotics, combined with administration of carob powder had a significant effect on these symptoms.

Conclusion

Therapy with TKI in patients with DTC is a promising new method for treatment of patients with radioiodine-refractory disease. Despite the marked adverse side effects, which can occur during the treatment with this type of medications, they have a strong potential for improving the prognosis of patients with advanced DTC.

Statement for Potential Conflicts of Interest: The authors declare that they have no potential conflicts of interest related to this research

References:

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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*. 2016 Jan;26(1):1–133.
2. Luo J, Gao B, Lin Z, Fan H, Ma W, Yu D, et al. Efficacy and safety of lenvatinib versus sorafenib in first-line treatment of advanced hepatocellular carcinoma: A meta-analysis. *Front Oncol*. 2022 Dec 22;12.
3. Granito A, Marinelli S, Negrini G, Menetti S, Benevento F, Bolondi L. Prognostic significance of adverse events in patients with hepatocellular carcinoma treated with sorafenib. *Therap Adv Gastroenterol*. 2016 Mar 3;9(2):240–9.

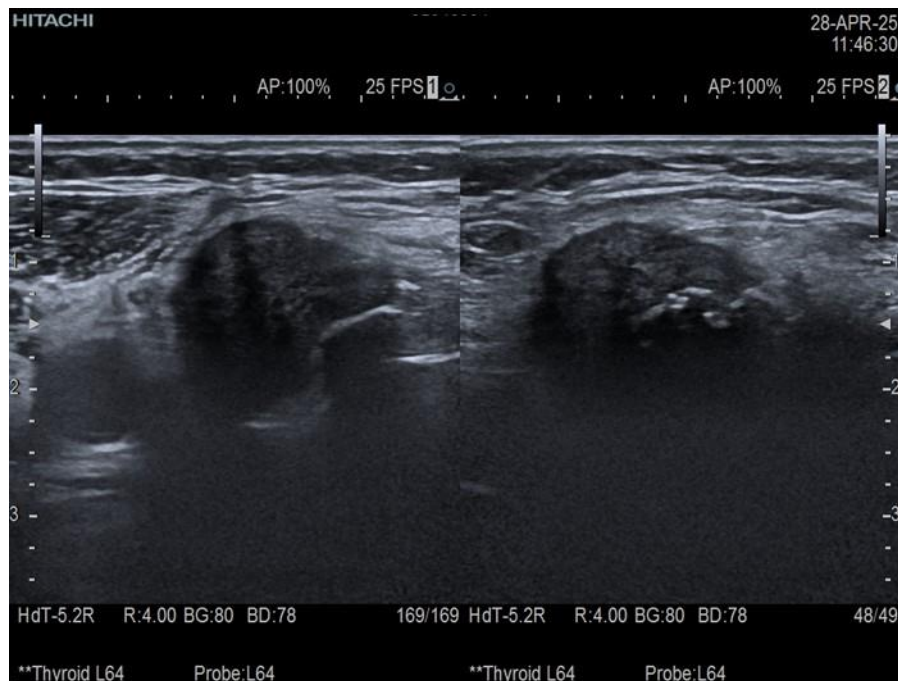


Fig. 1 Ultrasound image of the markedly hypoechoic pathological formation in the right thyroid lodge – transverse plane

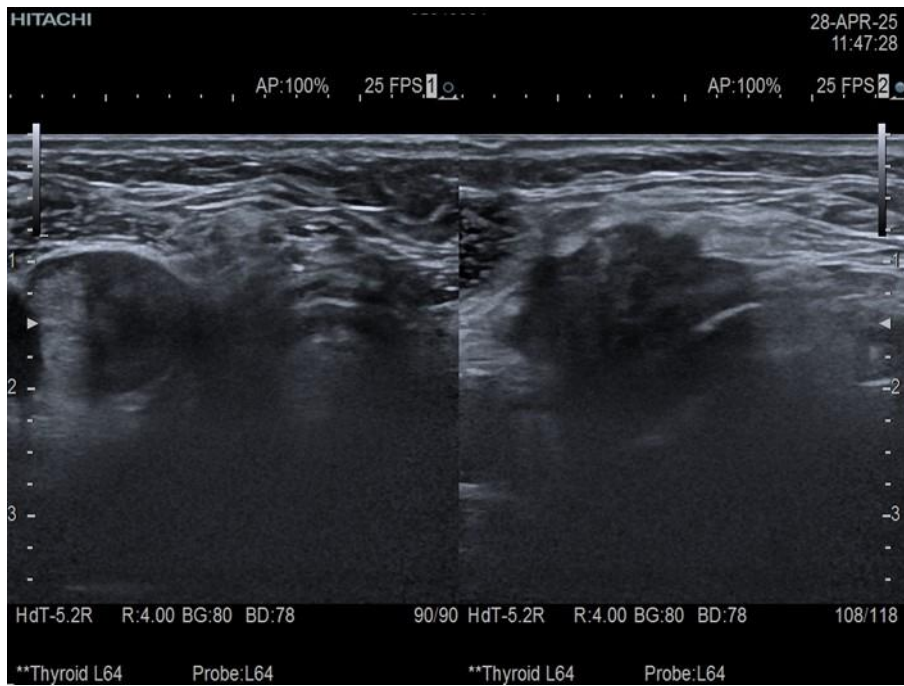


Fig. 2 Ultrasound image of the pathological formation in the right thyroid lodge, revealing irregular form and blurred margins –