Minerva Medica
EDIZIONI MINERVA MEDICA

Radioiodine-refractory thyroid cancer: a complex challenge

Journal: Minerva Medica
Paper code: Minerva Med-7845
Submission date: September 16, 2021
Article type: Editorial

Files:

1. Manuscript
   Version: 1
   Description: Text
   File format: application/vnd.openxmlformats-officedocument.wordprocessingml.document

Radioiodine-refractory thyroid cancer: a complex challenge

Running Title: Radioiodine-refractory thyroid cancer

Giovanni VITALE [1,2*], Giuseppe PELLEGRINO [3], Elio DESIDERIO [4], Luigi BARREA [5,6]

[1]Istituto Auxologico Italiano IRCCS, Laboratory of Geriatric and Oncologic Neuroendocrinology Research, Cusano Milanino (MI), Italy.

[2]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

[3]Postgraduation School in Radiodiagnostics, University of Milan, Via Festa del Perdono, 20122 Milan, Italy.

[4]Faculty of Medicine, University Federico II, Via Sergio Pansini 5, 80131 Naples, Italy; Naples, Italy.

[5]Dipartimento di Scienze Umanistiche, Università Telematica Pegaso, Via Porzio, Centro Direzionale, isola F2, 80143 Naples, Italy

[6]Centro italiano per la cura e il benessere del paziente con obesità (C.I.B.O), University Federico II, Via Sergio Pansini 5, 80131 Naples, Italy;

*Correspondence: giovanni.vitale@unimi.it

Differentiated thyroid cancer (DTC) accounts for more than 90% of thyroid cancers and has a typically favourable prognosis (10-year survival rate above 85%). During the last decades, the diagnosis of this tumor has made huge strides with the widespread use of neck ultrasonography, fine needle aspiration biopsy and genetic testing.[1-3] Indeed, DTC is the most frequent endocrine cancer and represents the most rapidly increasing human cancer worldwide.

Thyroidectomy is the mainstay of treatment for this disease. Postoperative radioactive iodine (RAI) therapy represents the "magic bullet" for a targeted treatment of DTC. RAI is used to ablate residual thyroid tissue, eliminate suspected micrometastases or known advanced disease. However, about 60-70% of patients with metastatic disease are or will become refractory to RAI. In patients with RAI-refractory DTC (RR-DTC) the 10-year survival rate drops to 10-20%.[4, 5] Although the management and follow-up of patients with DTC is quite well-standardized,[6] the occurrence of RAI resistance represents a complex challenge.[7]

In patients with RR-DTC and single lesion or few metastatic lesions within the same organ, loco-regional therapies (surgery, external-beam radiation therapy, radiofrequency ablation, and ethanol ablation or embolization) are suggested.[7, 8]

In patients with progressive or symptomatic plurimetastatic disease, medical therapy with multi-kinase inhibitors (MKIs) has been recently adopted. Sorafenib is a protein kinase inhibitor with activity against vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), rearranged during transfection (RET) and BRAF. Lenvatinib is a MKI targeting VEGFRs, fibroblast growth factor receptor (FGFR), PDFGR, stem cell factor receptor (KIT), and RET. Both sorafenib and lenvatinib prolonged progression-free survival compared with placebo in randomized phase 3 trials enrolling patients with RR-DTC. Indeed, sorafenib and lenvatinib are approved and used in daily clinical practice in several countries for patients with RR-DTC. Unfortunately, the toxicity of these compounds could have a detrimental effect on the quality of life of patients. Although randomized controlled trials comparing sorafenib with lenvatinib are not

available in patients with RR-DTC, their efficacy and side effect profiles appear comparable. However, the optimal timing of MKIs initiation and drugs selection have long been controversial. Future studies will need to better define the indications and timing for these systemic therapies in RR-DTC. In addition, the response of MKIs are not durable once patients stop taking the medications. Furthermore, resistance to MKIs has been reported after long-term use.[4,9]

Several other MKIs (cabozantinib, vandetanib, pazopanib, axitinib, anlotinib, etc) are available and have been recently adopted with encouraging results in phase I/II clinical trials in patients with RR-DTC.[4,9] This arsenal could be also used as a second line therapy in patients resistant to sorafenib or lenvatinib. Brose et al. reported a randomised, double-blind, placebo-controlled, phase 3 trial, enrolling 187 patients with RR-DTC who showed disease progression while taking prior MKIs. They were then administered cabozantinib (n=125) or placebo (n=62) with a significant improvement in progression-free survival after cabozantinib over placebo.[10]

One mechanism involved in the development RR-DTC is impairment of the sodium-iodine symporter through genetic alterations of the RTK/BRAF/MAPK/ERK and PI3K/AKT/mTOR pathways.[9] Indeed, BRAF is the most prevalent genetic alteration in metastatic RR-DTC patients. BRAF V600E mutant DTCs are more aggressive tumors and less responsive to RAI. Starting from these assumptions, strategies to re-sensitize tumors to RAI utilizing BRAF and MEK inhibitors (dabrafenib, vemurafenib and selumetinib) have been recently evaluated in small series of patients with RR-DTC, showing a direct antitumor-activity and an increase in RAI uptake in about 40-60% of patients.[9, 11]

Preliminary data are also available about the use of new compounds (pralsetinib, RXDX-105, selpercatinib, pioglitazone and larotrectinib) targeting chimeric kinases resulting by fusions or rearrangements in thyroid cancer cells, particularly RET fusions, PAX8/PPARγ, NTRK or ALK rearrangements. Interestingly, pralsetinib and selpercatinib showed an objective response in 89% and 79% of patients with RET fusion-positive thyroid cancer, respectively.[12, 13]

DTC has one of the lowest cancer mutational burdens. This renders DTC poorly immunogenic and less responsive to immunotherapy.[8]

In conclusions, the clinical management of RR-DTC represents a complex challenge requiring a multidisciplinary approach for the decision making of these patients by an expert panel. A precision medicine perspective could result in major improvements in RR-DTC, especially due to its complexity and interpatient variability. Future efforts should be dedicated:

- to clearly identify which drug to be used first and when a targeted therapy should be started on the bases of predictive biomarkers. These factors are strongly needed to customize treatment strategies. With the wide-spread application of genomic sequencing and greater understanding of predictive biomarkers this aim will hopefully be achieved.[14]
- to discover new potential targets.
- to the development of new animal models for RR-DTC, as recently achieved in other endocrine tumors, to perform high-throughput screening of novel anti-cancer drugs, as well as to test multi-targeted agents and combination therapies.[15]

References

1. Marturano I, Russo M, Malandrino P, Buscema M, La Rosa GL, Spadaro A, et al. Combined use of sonographic and elastosonographic parameters can improve the diagnostic accuracy in thyroid nodules at risk of malignancy at cytological examination. Minerva Endocrinol 2020;45:3-11.
2. Del Rio P, Cozzani F, Corcione L, Viani L, Loderer T, Rossini M. Correlation between cytological and histological findings in patients who underwent thyroidectomy. Predictive value and confounders. Minerva Endocrinol 2019;44:357-362.
3. Karapanou O. The role of molecular genetics in the presurgical management of thyroid nodules. Minerva Endocrinol (Torino) 2021;46:21-34.

4. Fukuda N, Takahashi S. Clinical Indications for Treatment with Multi-Kinase Inhibitors in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer. Cancers (Basel) 2021; 13(9):2279.
5. Colombo C. New perspectives in differentiated thyroid cancer Minerva Endocrinol (Torino) 2021;46:3-4.
6. Zhang L, Zou G. Role of thyroid ultrasound combined with thyroglobulin in the diagnosis of postoperative recurrence of thyroid cancer. Minerva Endocrinol 2019;44:192-198.
7. Gambale C, Elisei R, Matrone A. Management and follow-up of differentiated thyroid cancer not submitted to radioiodine treatment: a systematic review. Minerva Endocrinol 2020;45:306-317.
8. Colombo C, Giancola N, Fugazzola L. Personalized treatment for differentiated thyroid cancer: current data and new perspectives. Minerva Endocrinol (Torino) 2021;46:62-89.
9. Porter A, Wong DJ. Perspectives on the Treatment of Advanced Thyroid Cancer: Approved Therapies, Resistance Mechanisms, and Future Directions. Front Oncol 2021;10:592202.
10. Brose MS, Robinson B, Sherman SI, Krajewska J, Lin CC, Vaisman F, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2021;22:1126-1138.
11. Dunn LA, Sherman EJ, Baxi SS, Tchekmedyian V, Grewal RK, Larson SM, et al. Vemurafenib Redifferentiation of BRAF Mutant, RAI-Refractory Thyroid Cancers. J Clin Endocrinol Metab 2019;104:1417–28.
12. Subbiah V, Hu MI, Wirth LJ, Schuler M, Mansfield AS, Curigliano G, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol 2021;9:491-501.
13. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med 2020;383:825-835.

14. Pepe D, DE Keersmaecker K. Codon bias analyses on thyroid carcinoma genes. Minerva Endocrinol 2020;45:295-305.
15. Carra S, Gaudenzi G. New perspectives in neuroendocrine neoplasms research from tumor xenografts in zebrafish embryos. Minerva Endocrinol 2020;45:393-394.

NOTES

Conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Authors' contributions. GV was responsible for the concept of this paper and drafted the manuscript; GP, ED, and LB provided a critical review of the paper. All authors contributed to and agreed on the final version of the manuscript.

Acknowledgements. None