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AN EXPANDING CLASS IN THE TREATMENT OF THYROID CANCER: TYROSINE KINASE INHIBITORS

R. Dobrescu, C. Badiu*

"C.I. Parhon" National Institute of Endocrinology, Thyroid Related Disorders, Bucharest, Romania

Abstract

Thyroid cancer, the most frequent endocrine malignancy, is in most patients a treatable disease, with excellent outcome and cure rate. However, a few patients present with rapidly progressive metastatic differentiated thyroid cancer which loses the radioiodine uptake capacity. These rare cases are prone to a rapid evolution and poor prognosis. Medullary thyroid cancer is a neuroendocrine tumor occurring sporadically or as part of endocrine tumor syndromes, genetic tests being part of standard clinical evaluation. Current knowledge of tumor biology in thyroid cancer allowed development of a new class of drugs, thyrosine kinase inhibitors (TKI). Their use in clinical trials allowed the development of more specific drugs, increasingly effective and with less adverse reactions, interfering with multiple thyrosine kinase enzymes. Improvement of the progression free survival, decrease of tumor volume and tumor markers, as well as patients with stable disease on TKI are strong arguments for including patients in clinical trials. Currently, only four TKI are approved by FDA: sorafenib and lenvatinib for DTC; vandetanib and cabozantinib for MTC. In this paper we present this new class of drugs used in the treatment of aggressive thyroid cancer.

Key words: TKI, Lenvatinib, Thyroid cancer, Vandetanib, chemotherapy.

INTRODUCTION

Thyroid cancer is the most frequent endocrine neoplasia. The rapidly expanding number of cases is related to technical development in ultrasound detection (ultrasound and elastography) as well as improvement in pathology diagnosis (FNAB) assisted in selected cases by genetic molecular tools. Follicular epithelium could be the source of several types of differentiated thyroid cancer (DTC), from the most frequent, papillary cancer with its variants, to the follicular and seldom but very aggressive, anaplastic thyroid cancer. Standard treatment includes thyroidectomy and radioiodine ablation, followed by thyroxin substitutive - suppressive treatment. Thyroid parafolicular cells are the source of medullary thyroid cancer (MTC), which could appear in its sporadic or familial form. The genetic basis of familiar MTC requires the molecular screening for ret gene mutations to find unaffected individuals who might require prophylactic thyroidectomy. Despite many advances in thyroid cancer diagnosis and treatment, the presence of unresectable recurrences and insensitivity to radioactive iodine leads to therapeutic challenges and poorer outcomes. This includes differentiated thyroid carcinoma which have lost radioiodine uptake capacity, or metastatic MTC. For these cases, thyroid kinase inhibitors are a new hope.

Thyrosine kinase enzymes are involved in activation by phosphorylation of proteins which act as a signal transduction cascade. These enzymes are blocked by small molecules called tyrphostins or thyroid kinase inhibitors. Originally described by Yaish *et al.* in 1988 in Science (1) in relation to epidermal growth factor receptor, now the class is widely used in oncology. The pathogenesis of thyroid cancer implies multiple genetic alterations in key pathways involving receptor tyrosine kinases (RTKs) and the MAPK cascade. Along the last decade, multikinase inhibitors (MKI) were developed for the treatment of refractory metastatic thyroid cancer.

Multikinase inhibitors

Currently, there are four drugs approved by the FDA: two used in the treatment of DTC (sorafenib and lenvatinib) and 2 for MTC (vandetanib and cabozantinib). Indication of use refers to progressive, multimetastatic disease with impact upon quality of life (QOL) or life-threatening lesions (2). During treatment, disease stabilization or partial response could occur for 1-3 years. However, persistent disease with stable metastatic lesions (according to RECIST 1.1 criteria) and stable tumor markers should not automatically lead to MKI prescription. Factors against MKI prescription

*Correspondence to: Corin Badiu MD, PhD, National Institute of Endocrinology, Thyroid Related Disorders, Aviatorilor 34-36, Bucharest, 011863, Romania, E-mail: badicrin@yahoo.co.uk

are patients with stable lesions, asymptomatic with a good QOL, and constant values of tumor markers in similar conditions for DTC (thyroglobulin, either on thyroxine or stimulated) or for MTC calcitonin / carcinoembryonic antigen, respectively. MKI are not devoid of adverse reactions which impact upon QOL and could even bring life threatening complications. Patients enrolled in trails typically receive therapy until disease progression and development of resistance or until development of severe adverse effects.

Sorafenib is a MKI acting upon VEGFR1–3, Flt-3, KIT, RET, and CRAF/BRAF. Since these mechanisms are important in promoting thyroid oncogenesis, several prospective phase II trials bring hope in terms of a response rate and stable disease in PTC of 50-80%, while non PTC has a much lower response rate (3). No doubt, the study bringing most evidence was DECISION phase III trial on 417 cases (57% PTC, 25% FTC, 10% PDTC) who were randomized to sorafenib 400 mg/12 h (N = 207) or placebo (N = 210) until disease progression (4). The treatment arm presented a double progression free survival (PFS) time as compared with placebo (10.8 *vs.* 5.8 months), independent of other variables (age, sex, pathology, mutations).

Lenvatinib

Lenvatinib is a MKI inhibitor that is upregulated in follicular thyroid cells and is involved in tumor progression through MAPK signaling pathway activation. Administered orally, it inhibits VEGFR 1, 2, and 3, FGFR1 through 4, PD-GFR alpha, RET, and KIT. The SELECT trial, a placebo controlled, double blind interventional study included 392 patients with progressive radioiodine-refractory DTC randomized to lenvatinib 24 mg daily (N =261) or placebo (N = 131) (5). Patients under placebo could receive open-label lenvatinib if disease progression was documented. PFS was of 18.3 months *vs.* 3.6 months in the placebo group, while response rate was of 64.8% under lenvatinib *vs.* 1.5% in the placebo arm. An important proportion presented grade 3 or higher treatment-related adverse effects like hypertension and proteinuria, leading to dose reduction. Mutation status analysis (BRAF and RAS) did not change the survival benefit. In our experience, three cases of 131I refractory DTC were enrolled in the SELECT study and are currently under lenvatinib treatment, with excellent progression free survival.

Vandetanib

Vandetanib is a potent tyrosine kinase inhibitor (TKI) that competes with the adenosine triphosphate (ATP) binding site in the catalytic domain of RET, VEGFR2–3 and EGFR, being the first drug approved for MTC. First evidence started with experiments on transfected cells in 2002 (6), then moved to phase I clinical trials showing a safety dose of 300 mg/day (7). A phase III trial included 331 patients with unresectable locally advanced or metastatic MTC receiving vandetanib 300 mg per day until disease progression (8). PFS was 19.3 months in the placebo arm and predicted median of 30.5 months in the vandetanib arm. The most significant adverse effect was grade 3 and over QTc prolongation observed in 19 patients. Patients with sporadic MTC harboring a RET mutation, particularly the M918T mutation, benefited from vandetanib.

Cabozantinib

Cabozantinib is a potent ATP competitive inhibitor of VEGFR2, MET, KIT and RET approved for the treatment of progressive advanced MTC. The first study of cabozantinib use was performed in 37 patients with metastatic MTC, 41% of which showed stable disease. Several adverse effects were documented at doses of 250 mg daily, such as the hand–foot syndrome, mucositis and alanine transaminase and lipase elevations. The promise of this first study allowed a larger phase III clinical trial conducted on 330 cases with locally advanced or metastatic MTC with documented RECIST progression. Patients were randomly assigned to cabozantinib 140 mg per day or placebo until disease progression or unacceptable toxicity (9). The study shows a longer PFS in the cabozantinib group compared with placebo (11.2 months *versus* 4.0 months). A significant correlation was detected between individual changes in calcitonin at week 12 and radiological response of target lesions at week 12, only in patients treated with cabozantinib ($p < 0.0001$).

Other TKI

A number of other molecules are now in clinical trials, trying to use TKI in selected populations with DTC or MTC according to mutation analysis (10).

Motesanib is an inhibitor of VEGF receptors, platelet-derived growth-factor receptor, and KIT. It was evaluated in a phase II trial of 93 patients with progressive, unresectable or radioiodine resistant disease. Progression-free survival was 9.3 months,

14% of patients achieved PR and 67% SD; 81% had a decrease in thyroglobulin and 87% had tumor shrinkage. The most common adverse events reported were diarrhea (59% of patients), hypertension (56%), fatigue (46%), and weight loss (40%) (11).

Pazopanib similarly targets VEGF receptors, platelet-derived growth factor, and c-KIT. It has been evaluated in a phase II trial of 39 patients with metastatic, rapidly progressive radioiodine resistant DTC. 49% of patients showed PR and median PFS was 11.7 months. Grade 3 adverse events were noted in 57% of patients, and two patients died during the trial of myocardial infarction and bowel perforation, both of which are associated with VEGF inhibition (12). A similar phase II trial of 35 patients with advanced, progressive MTC documented PR in 14.3% of patients, median PFS of 9.4 months and overall survival of 19.9 months. The most frequent side effects were hypertension (33%), fatigue (14%) and diarrhea (9%) (13).

Sunitinib targets the vascular endothelial growth factor receptor (VEGFR) types 1 and 2, platelet-derived growth factor receptors, c-KIT, FLT3, and RET, and is thus thought to have potential in both DTC and MTC. It was evaluated in two phase II clinical trials: Carr *et al.* enrolled 35 patients with FDG-avid, radioiodine resistant DTC and 7 patients with medullary thyroid cancer. One patient achieved CR, 28% had PR, and 46% had SD; median time to progression was 12.8 months (14). In the second trial Cohen *et al.* recruited 43 patients with DTC and MTC with progressive disease, resistant to surgery, external radiotherapy and radioiodine ablation. SD was noted in 68%, and 13% had PR (15).

Dabrafenib, a selective BRAF inhibitor, is currently being evaluated as part of a strategy to increase radioiodine uptake in patients with radioiodine resistant DTC. In a study of 10 patients with BRAF V600E-mutant iodine-refractory PTC, six patients (60%) demonstrated new radioiodine uptake on whole body scan after treatment with dabrafenib. After treatment with 5.5 GBq iodine-131, two patients had partial responses and 4 patients had stable disease at 3 months; 4 of the 6 treated patients had decreased thyroglobulin levels (16).

In conclusion, tyrosine kinase inhibitors are a new hope for rare cases of thyroid cancer patients with aggressive, multimetastatic and progressive tumors which have lost the capacity of radioiodine uptake.

Their development could improve progression-free survival, stable disease and sometimes even promote a decrease in tumor volume and plasma levels of molecular markers (thyroglobulin in DTC or calcitonin in MTC). Genetic specific TKI could ensure the selection of a more responsive population and improve the outcomes. Enrolling patients in therapeutic trials using TKI for treatment of rapidly progressive DTC or metastatic MTC represents an important alternative to classic, nonspecific chemotherapy, when all other treatments are tried without success.

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References

1. Yaish P, Gazit A, Gilon C, Levitzki A. Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. Science 1988; 242(4880):933-935.
2. Bible KC, Cote GJ, Demeure MJ, Elisei R, Jhiang S, Ringel MD. Correlative Studies in Clinical Trials: A Position Statement From the International Thyroid Oncology Group. J Clin Endocrinol Metab 2015;jc20152818.
3. Alonso-Gordoa T, Diez JJ, Duran M, Grande E. Advances in thyroid cancer treatment: latest evidence and clinical potential. Ther Adv Med Oncol 2015; 7(1):22-38.
4. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014; 384(9940):319-328.
5. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las HB, Zhu J, Sherman SI. Lenvatinib *versus* placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015; 372(7):621-630.
6. Carlomagno F, Vitagliano D, Guida T, Basolo F, Castellone MD, Melillo RM, Fusco A, Santoro M. Efficient inhibition of RET/papillary thyroid carcinoma oncogenic kinases by 4-amino-5-(4-chloro-phenyl)-7-(t-butyl)pyrazolo[3,4-d]pyrimidine (PP2). J Clin Endocrinol Metab 2003; 88(4):1897-1902.
7. Tamura T, Minami H, Yamada Y, Yamamoto N, Shimoyama T, Murakami H, Horiike A, Fujisaka Y, Shinkai T, Tahara M, Kawada K, Ebi H, Sasaki Y, Jiang H, Saijo N. A phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. J Thorac Oncol 2006; 1(9):1002-1009.
8. Wells SA, Jr., Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012; 30(2):134-141.
9. Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013; 31(29):3639-3646.
10. Gruber JJ, Colevas AD. Differentiated thyroid cancer: focus on emerging treatments for radioactive iodine-refractory patients.

Oncologist 2015; 20(2):113-126.
11. Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Schlumberger MJ. Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 2008; 359(1):31-42.
12. Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, Rubin J, Sideras K, Morris JC, III, McIver B, Burton JK, Webster KP, Bieber C, Traynor AM, Flynn PJ, Goh BC, Tang H, Ivy SP, Erlichman C. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol 2010; 11(10):962-972.
13. Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, Rubin J, Karlin N, Sideras K, Morris JC, III, McIver B, Hay I, Fatourechi V, Burton JK, Webster KP, Bieber C, Traynor AM, Flynn PJ, Cher GB, Isham CR, Harris P, Erlichman C. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. J Clin Endocrinol Metab 2014; 99(5):1687-1693.
14. Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM, Bauman JE, Martins RG. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res 2010; 16(21):5260-5268.
15. E. E. Cohen, B. M. Needles, K. J. Cullen, S. J. Wong, J. L. Wade III, S. P. Ivy, V. M. Villaflor, T. Y. Seiwert, K. Nichols, E. E. Vokes. Phase 2 study of sunitinib in refractory thyroid cancer. J Clin Oncol 2008;26 suppl:6025a.
16. Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res 2015; 21(5):1028-1035.