

An internist's approach to cancer diseases based on the model of thyroid cancer treated with tyrosine kinase inhibitors

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New treatment options have come along the discovery of different tyrosine kinases and their crucial role in the pathogenesis of several cancers, including thyroid carcinoma. Multikinase inhibitors (MKIs) are a new group of drugs, recently widely investigated in oncology. They show activity against receptors of different growth factors, leading to the inhibition of tumor cell growth and division.

Thyroid cancer is the most common endocrine malignancy. According to the Polish National Cancer Registry, it accounts for 0.5% and 2.6% of all neoplasms in men and women, respectively. The number of new cases of thyroid cancer has recently rapidly increased worldwide, mostly due to accurate and easily accessible thyroid sonography. In Poland, thyroid cancer was diagnosed in 314 patients in 1980, 448 patients in 1990, and as many as 2192 patients in 2010.

The most common is differentiated thyroid cancer (DTC), diagnosed in nearly 94% of patients (80%, papillary thyroid cancer [PTC] and 14%, follicular thyroid cancer [FTC]) and arising from follicular cells. Medullary thyroid carcinoma (MTC), which develops from parafollicular C cells, accounts for 4% to 8% of all cases of thyroid cancer. In general, both DTC and MTC are characterized by good outcomes, with 10-year overall survival (OS) rates of 93%, 85%, and 75% for PTC, FTC, and MTC, respectively.¹

Regardless of its good prognosis, approximately 3% to 15% of DTC patients show disseminated disease at presentation,^{2,3} whereas DTC relapse may occur during decades in up to 30% of patients.⁴ Surgery and/or radioiodine (RAI) therapy are the main treatment options for recurrent DTC,^{5,6} as the majority of patients show the ability of RAI uptake in cancer foci.⁷ However, one-third of patients are refractory to RAI therapy. This group is characterized by much worse prognosis, with OS rates of about 10% at 10 years and 6% at 15 years.⁷

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Received: October 14, 2016.
Accepted: October 14, 2016.
Published online:
November 30, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (11): 925-928
doi:10.20452/pamw.3677
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Considering MTC, distant metastases are present in 7% to 23% of patients at diagnosis or develop during subsequent follow-up.⁸ This group shows significantly poorer outcomes in comparison with patients diagnosed at early stages of the disease, with 10-year survival of 50% and 70%–80%, respectively.⁹ Persistent elevated serum calcitonin levels (a very sensitive MTC biochemical marker) after surgery is observed in 80% of patients with palpable MTC and in 50% of those with nonpalpable macroscopic MTC, regardless of a radical surgical approach.¹⁰ Recurrence is seen in more than 50% of these patients during a mean 10-year follow-up.¹⁰

Until recently, therapeutic options for advanced RAI-refractory DTC and inoperable or disseminated MTC were mainly based on radiotherapy and local treatment (radiofrequency ablation, embolization, etc.). The outcomes of different schemes of chemotherapy were disappointing; therefore, it is no longer recommended in DTC or MTC.^{5,6,11,12}

To date, 4 different MKIs have demonstrated their activity against thyroid cancer in randomized, placebo-controlled phase III studies and have been approved by the US Food and Drug Administration (FDA) and European Medical Agency (EMA): sorafenib (Nexavar, Bayer)¹³ and lenvatinib (Lenvima, Eisai)¹⁴ in RAI-refractory DTC, and vandetanib (Caprelsa, Genzyme)¹⁵ and cabozantinib (Cometriq, Ipsen)¹⁶ in MTC.

Sorafenib is an oral inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, 3, RET, RAF, and platelet-derived growth factor receptor (PDGFR) β . Its efficacy in progressive advanced, RAI-refractory DTC has been proved in the DECISION trial that enrolled 417 patients randomly allocated in a 1:1 ratio to either sorafenib or placebo. Sorafenib compared with placebo significantly prolonged progression free survival (PFS), 10.8 months and 5.8 months, respectively (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.45–0.76; $P < 0.0001$).¹³ No significant impact on OS has been observed either in primary or in delayed analysis.^{13,17} However, considering the effect on OS, we have to remember that upon progression, patients who received placebo were allowed to crossover to open-label sorafenib.

Lenvatinib is also a potent oral inhibitor of VEGFR 1, 2, 3, PDGFR α , fibroblast growth factor receptor 1, 2, 3, 4, RET, and KIT. Phase III trial (SELECT), which demonstrated its effectiveness, involved 392 patients, and as in the DECISION study with progressive advanced, RAI-refractory DTC, it randomly assigned to a lenvatinib or placebo group at a ratio of 2:1. Patients on placebo, who progressed in a blinded phase, could receive open-label lenvatinib. The median PFS in patients who were given lenvatinib was significantly longer than in those receiving placebo: 18.3 months and 3.6 months, respectively (HR, 0.21; 95% CI, 0.14–0.31; $P < 0.001$).¹⁴ The global differences in OS between lenvatinib and placebo groups were not significant.^{14,18} However, in

the group of patients above 65 years of age in comparison to placebo the impact of lenvatinib administration on OS was significant (HR, 0.53; 95% CI, 0.31–0.91; $P = 0.02$).¹⁸

Vandetanib is an oral MKI that selectively inhibits RET, VEGFR, and endothelial growth factor receptor. The ZETA trial, a randomized, placebo-controlled phase III study, which led to drug approval, included 331 patients with locally advanced or metastatic MTC. Patients (with sporadic and hereditary MTC) were randomly allocated to receive vandetanib or placebo at a ratio of 2:1. The requirement of MTC progression was not listed among the inclusion criteria. Upon progression, patients were given vandetanib under the open-label phase of the study. Patients treated with vandetanib showed significantly longer PFS than those from the placebo arm: 30.5 months and 19.3 months, respectively (HR, 0.46; 95% CI, 0.31–0.69; $P = 0.001$).¹⁵ There were no significant differences regarding OS.¹⁵

Cabozantinib is another MKI approved for advanced MTC. It demonstrates the activity against VEGFR2, RET, and MET. Its beneficial effect on the course of MTC was shown by the EXAM trial, a phase III, placebo-controlled, randomized study. A total of 330 patients with MTC, both the sporadic and hereditary forms, were randomly administered cabozantinib or placebo at a ratio of 2:1. Contrary to all of the above studies, crossover was not allowed. Treatment with cabozantinib resulted in a significant prolongation of PFS, when compared with placebo. The median PFS were 11.2 months and 4.0 months, respectively (HR, 0.28; 95% CI, 0.19–0.40; $P < 0.001$).¹⁶ In the whole group, OS was not significantly different between patients receiving cabozantinib and those receiving placebo.^{16,19} However, in a subgroup of MTC patients with the RET M918T mutation in tumor cells, the differences in OS were significant: 44.3 months and 18.9 months, respectively (HR, 0.6; 95% CI, 0.38–0.95; $P < 0.026$).²⁰

Despite the beneficial effect of all the above drugs on PFS, and in selected patients also on OS, we have to be aware that MKI-targeted therapy is a palliative treatment and therefore its potential impact on the quality of life seems to be particularly important. Each drug caused a variety of adverse reactions in nearly all treated patients, leading to a dose reduction in 35%, 79%, 64.3%, and 67.8% or withdrawal in 12%, 16%, 18.8%, and 14.2% of the patients who were given vandetanib, cabozantinib, sorafenib, and lenvatinib respectively.^{13–16} All these agents are VEGFR inhibitors that may result in similar complications related to VEGFR blockade, including hypertension, proteinuria, impaired wound healing, gastrointestinal perforation, hemorrhage, thrombosis, reversible posterior encephalopathy, heart failure, and osteonecrosis. Other common complications seen in patients receiving MKI are diarrhea, gastrointestinal disorders, skin reactions (rashes, acne, hand-foot syndrome, etc.), fatigue, and weight loss. The majority of treatment-related adverse

events fulfilled G1 (mild) and G2 (moderate) criteria according to the Common Terminology Criteria for Adverse Events (CTCAE). However, some of them, although rare, were classified as G3 (serious), G4 (life-threatening), or even G5 (fatal), including bleeding, pulmonary embolism, arterial and venous thrombosis, heart failure, QTC prolongation, gastrointestinal perforation or fistula formation, hepatotoxicity, and various laboratory abnormalities.¹³⁻¹⁶ In our opinion, the management of MKI-related side effects is a challenge for internists, especially in case of G3 and G4 events, when the early recognition, immediate reaction, and ability to make prompt clinical decisions may prevent serious and permanent complications, or even save the patient's life.

Our 10-year experience with the use of MKIs in more than 140 patients with thyroid carcinoma has changed our approach from enthusiastic at the beginning, as we were now able to offer a new therapeutic modality to patients who previously could receive only symptomatic treatment, to cautious, when we became aware of the possible complications of the therapy. Based on a meta-analysis of 10 randomized trials carried out in patients with different cancers, the risk of therapy-related death in patients who are given a VEGFR inhibitor is about 1.5% to 2% with a relative risk of 2.23 (95% CI, 1.12–4.44; $P = 0.023$) compared with controls receiving placebo.²¹ The cardiovascular issue is particularly important in thyroid cancer as it has been demonstrated that patients with general DTC have an increased risk of cardiovascular mortality (HR, 3.35; 95% CI, 1.66–6.74).²² Therefore, considering the risk–benefit ratio, MKIs are currently recommended by the newest American Thyroid Association guidelines for a narrow group of patients with RAI-refractory DTC or MTC presenting “imminently threatening disease progression expected to require intervention and/or to produce morbidity or mortality in <6 months; symptomatic disease or diffuse disease progression as opposed to focal progression”.⁶

We believe that a close cooperation between oncologists and internists should be a gold standard in comprehensive clinical care in oncology. It seems to be particularly important in the era of immunotherapy and targeted drugs, which has obviously brought about new treatment options for patients with various advanced malignant tumors, but at the same time it has faced us with a challenge of how to manage the side effects. On one hand, a cautious approach presented by oncologists is essential to answer the question “who and when should be treated”. It is well known that neoplastic disease, even recurrent or disseminated, does not in itself constitute an unequivocal indication for treatment. So called “watchful waiting” is widely accepted in oncology because a neoplastic disease may be stable without any intervention, sometimes—as in the course of thyroid cancer—even for years. On the other hand, the possible serious complications of

treatment, particularly regarding new targeted drugs, require rather an internist's approach based on close monitoring, knowledge of differential diagnosis, and sometimes immediate rescue therapy in the case of severe and life-threatening adverse reactions. Therefore, we call oncologists for cooperation with internists, which in our opinion is the optimal way of patient care.

Acknowledgments The project was supported by the Polish National Center of Research and Development MILESTONE project – Molecular diagnostics and imaging in individualized therapy for breast, thyroid, and prostate cancer, grant no. STRATEGMED 2/267398/4/NCBR/2015.

Note The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

REFERENCES

- Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer*. 1998; 83: 2638-2648.
- Sampson E, Brierley JD, Le LW, et al. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. *Cancer*. 2007; 110: 1451-1456.
- Nixon IJ, Whitcher MM, Palmer FL, et al. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. *Thyroid*. 2012; 22: 884-889.
- Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 1994; 97: 418-428.
- Jarżab B, Dedecjus M, Handkiewicz-Junak D, et al. Diagnostics and Treatment of Thyroid Carcinoma. *Endokrynol Pol*. 2016; 67: 74-107.
- 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*. 2016; 26: 1-133.
- Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab*. 2006; 91: 2892-2899.
- Massicotte MH, Brassard M, Claude-Desroches M, et al. Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: a retrospective study of the TUTHYREF network. *Eur J Endocrinol*. 2014; 170: 575-582.
- Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. *Cancer*. 2006; 107: 2134-2142.
- Tuttle R, Ball D, Byrd D, Al E. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). Thyroid Carcinoma. NCCN Guidelines. 2013; Version 2.
- Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009; 19: 565-612.
- Schlumberger M, Bastholt L, Dralle H, et al. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J*. 2012; 1: 5-14.
- Brose MS, Nutting CM, Jarżab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet*. 2014; 384: 319-328.
- Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. *N Engl J Med*. 2015; 372: 621-630.
- Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol*. 2012; 30: 134-141.
- Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol*. 2013; 31: 3639-3646.
- Brose M, Jarżab B, Elisei R, et al. Updated overall survival analysis of patients with locally advanced or metastatic radioiodine-refractory differentiated thyroid cancer treated with sorafenib on phase 3 DECISION trial (ABSTRACT). *J Clin Oncol*. 2014; 32 (Suppl): 6060.

- 18 Brose M, Schlumberger M, Tahara M, et al. Effect of age and lenvatinib treatment on overall survival for patients with 131I-refractory differentiated thyroid cancer in SELECT. *J Clin Oncol*. 2015; 33 (Suppl): abstr 6048.
- 19 Schlumberger M, Elisei R, Muller S, et al. Final overall survival analysis of EXAM, an international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib in medullary thyroid carcinoma patients with documented RECIST progression at baseline. *J Clin Oncol*. 2015; 33: 6012.
- 20 Sherman S, Elisei R, Mueller S, et al. The Impact of RET and RAS Mutation Status on Overall Survival in the EXAM Trial, a Phase 3 Study of Cabozantinib in Patients with Progressive, Metastatic Medullary Thyroid Cancer (MTC). In: ITC Annual Meeting, Orlando, FL, USA; 18-23. 2015.
- 21 Schutz FA, Je Y, Richards CJ, Choueiri TK. Meta-analysis of randomized controlled trials for the incidence and risk of treatment-related mortality in patients with cancer treated with vascular endothelial growth factor tyrosine kinase inhibitors. *J Clin Oncol*. 2012; 30: 871-877.
- 22 Klein Hesselink EN, Klein Hesselink MS, de Bock GH, et al. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. *J Clin Oncol*. 2013; 31: 4046-4053.