EDITORIAL OPEN ACCESS

Multikinase inhibitors in the setting of thyroid carcinoma

Maria João Bugalho

INTRODUCTION

Most thyroid carcinomas are well differentiated (DTC) and include the papillary (PTC) and follicular (FTC) histological types. As they derive from the follicular cells maintain the ability to take up and organify iodine. A small percentage of cases loose the features of the cell of origin and are classified as poorly differentiated (PDTC) or undifferentiated/anaplastic (ATC) the least common and most aggressive of all thyroid carcinomas. Although ATC may derive de novo, many cases seem to arise from preexisting PTC or FTC.

Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular (also called C cells) cells of the thyroid that originate from the neural crest and accounts for approximately 5% of thyroid carcinomas.

The majority of DTC is effectively treated by surgery, radioactive iodine (RAI) and TSH suppressive levothyroxine. Despite the good outcome and low mortality rates, local recurrence occurs in up to 20% of patients and distant metastases in approximately 10% at 10 years [1, 2] with half being detectable at initial disease presentation. Management of metastatic disease may include targeted surgeries, external beam radiotherapy and further treatments with RAI. However some become radioiodine-refractory representing a therapeutic challenge.

Primary treatment of MTC patients relies on surgery that is the only potentially curable treatment, since "C" cells have not the ability to uptake and/or organify iodine. The 10-year survival rates are around 40–50%. Systemic chemotherapy and radiation therapy are not believed to represent important or useful options for most patients with metastatic MTC.

Anaplastic thyroid carcinoma is one of the most aggressive solid tumors known to have a poor prognosis and a median survival of less than six months. Many patients present with inoperable disease and complete resection is possible for only up to one-third of patients at presentation [3].

Independently of the histological type, for patients with rapidly progressive, locally advanced or metastatic disease systemic chemotherapy and external beam radiotherapy have been used with disappointing results.

The use of kinase inhibitors is evolving based on understanding of the pathways involved in thyroid cancer. The rationale for their use relies in the fact that several targets of these drugs are thyroid specific oncogenes involved in pathogenesis and progression of disease. Moreover, these drugs inhibit several kinases involved in angiogenesis thus acting as anti-angiogenic drugs.

A meta-analysis [4] documented modest objective responses for patients with differentiated thyroid carcinoma and more favorable for patients with medullary thyroid carcinoma, whereas side effects of kinase inhibitors are not negligible. A new section on "Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer" was added to the NCCN Guidelines to assist with using these novel targeted agents [5].

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DIFFERENTIATED THYROID CARCINOMA

PTC is driven by RET rearrangements, activating point mutations in the BRAF and activating point mutations in the RAS oncogenes (limited to PTC follicular variant).

FTC is frequently associated with Ras point mutations, rearrangements between the Pax8 transcription factor and the peroxisome proliferator-activated receptor γ (*PPARγ*) and mutations involving the phosphatidylinositol 3-kinase (PI3K)–Akt pathway.

A growing understanding of the molecular basis of thyroid cancer particularly the identification of key oncogenic mutations has allowed the development of targeted agents in different types of advanced thyroid carcinoma. Among the most successful agents are different kinase inhibitors.

Different collaborative placebo-controlled multicenter trials [6–10] to determine the efficacy of Sorafenib, a multikinase inhibitor, in patients with advanced DTC, have documented improvement in progression-free survival. Yet no medium or long beneficial effects were found. The most common adverse events related to sorafenib treatment include hand–foot skin reaction, rash (often occurring as a papular, erythematous eruption that can involve extremities as well as the trunk), upper and lower gastrointestinal (GI) distress, weight loss, fatigue and hypertension. More serious is the development of squamous cell carcinomas of the skin after treatment with Sorafenib [11, 12]. One case of lung squamous cell carcinoma was also reported in association with Sorafenib [13].

The U.S. Food and Drug Administration (FDA) approved Sorafenib for radioiodine-resistant metastatic DTC (November 2013).

More recently (February 2015), Lenvatinib (a multitargeted tyrosine kinase inhibitor) was also approved for the same indication. The approval was based on the demonstration of improved progression free survival (PFS) in the Phase III SELECT trial. Median PFS was 18.3 months in the lenvatinib arm and 3.6 months in the placebo arm. Objective response rates were 65% and 2% in the lenvatinib and placebo arms, respectively [14]. Lenvatinib targets VEGFR1-3, FGFR1-4, RET, c-Kit and PDGRR-ß. The inhibition of FGFRs offers an opportunity to overcome resistance to VEGF/VEGFR inhibitors.

The most common side effects associated with Lenvatinib were weight loss, hypertension, proteinuria, diarrhea, palmar-plantar erythrodysesthesia syndrome and dysphonia. The most serious adverse reactions were cardiac failure, arterial thrombotic events, hepatotoxicity, dehydration, renal failure, gastrointestinal perforation. In the Lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related [14].

Assessment of serum levels of circulating cytokines and angiogenic factors in patients under Lenvatinib [15] led to the observation that lower baseline levels of angiopoietin-2 were suggestive of tumor response and longer PFS. Further studies are necessary to establish the clinical usefulness of this type of markers towards a pre-treatment selection of good responders.

Another interesting development has been the discovery that selumetinib appears to induce re-differentiation of RAI resistant thyroid cancers [16].

MEDULLARY THYROID CARCINOMA

A subset of MTC cases is hereditary and due to germline mutations in the RET tyrosine kinase receptor gene. Somatic mutations in either RET or RAS are also present in most sporadic tumors.

Metastatic disease is not curable, however, metastatic disease can be quite indolent and decision to initiate therapy may be difficult.

In 2011, the FDA approved vandetanib (which targets RET, epidermal growth factor receptor, and vascular endothelial growth factor receptor) for the treatment of patients with symptomatic or progressive, locally advanced, or metastatic MTC. The approval was based on an international multicenter randomized double-blind trial, the Zactima Efficacy in Thyroid Cancer Assessment (ZETA) phase III study, conducted in patients with unresectable locally advanced or metastatic MTC [17]. The ZETA study showed a significant prolongation of PFS with vandetanib versus the placebo (hazard ratio, 0.46; 95% CI, 0.31 to 0.69; $p < .001$). Statistically, significant advantages for vandetanib were also seen for objective response rate, disease control rate, and biochemical response.

Diarrhea, nausea, rash, hypertension, headache, fatigue, anorexia and abdominal pain are the most commonly reported adverse events. The QTc interval prolongation is considered the most stressed cardiac adverse event associated with this drug [18]. However, cardiomyopathy leading to fatal acute cardiac failure is also a possible and severe complication; it was associated with cardiomyocyte hypertrophy and marked myocyte degeneration in the subendocardial zones and papillary muscles of the myocardium [19].

Recently, Chougnet et al. [20] analyzed the toxicity profile and efficacy of vandetanib treatment when given outside any trial. Data from 60 MTC patients was analyzed. Median progression-free survival was 16.1 months. Twenty-five patients discontinued treatment for disease progression (range 0.3–29 months). Best tumor response was a complete response in one patient, a partial response in 12 (20%), stable disease in 33 (55%), and progression in seven patients (12%). All patients had at least one adverse event during treatment. The main adverse events were skin toxicity, diarrhea, and asthenia. Sixteen patients (27%) discontinued treatment for toxicity, and one patient died from vandetanib-induced cardiac toxicity.

In 2012, the FDA also approved cabozantinib for the same indication on the basis of the Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) trial [21]. Cabozantinib is a tyrosine kinase inhibitor that targets three potentially important pathways in MTC: MET, vascular endothelial growth factor receptor 2, and RET. Results from the EXAM study documented a median PFS of 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40; $p < .001$). Objective tumor response rates and biochemical responses were also significantly improved with cabozantinib. Most common grade 3 or 4 adverse events were diarrhea, hand-foot syndrome, and fatigue. Grade 5 adverse events included fistula, respiratory failure, sudden death, hemorrhage, sepsis, and cardiopulmonary failure.

RET-activating mutations at codon 804 or 806 (V804M/L, Y806C) cause resistance to some kinase inhibitors, such as vandetanib and V804M causes resistance to cabozantinib as well.

Ponatinib, a multitargeted kinase inhibitor that was recently approved for treatment of refractory Philadelphia-positive leukemia, revealed potent inhibition of oncogenic RET including the vandetanib-insensitive V804M/L mutants [22].

MEDULLARY THYROID CARCINOMA AND CUSHING'S SYNDROME

Ectopic Cushing's syndrome accounts for approximately 10% of all types of Cushing's syndrome and is mainly due to small cell lung carcinoma or bronchial carcinoids. Abnormalities associated with Cushing's syndrome are often life-threatening. Ectopic Cushing's syndrome has been described associated with the secretion of adrenocorticotropic hormone (ACTH) and/or corticotrophin-releasing factor (CRF) by the C cells [23]. A few cases of ectopic Cushing's syndrome in patients with MTC with a remarkable response to kinase inhibitors were reported [24–27]. Hypokalemia, generally present in patients with ectopic Cushing's syndrome, increases the risk for prolonged QT and torsades de pointes. For this reason, vandetanib is particularly dangerous and should not be the first choice.

The mechanism explaining inhibition of ectopic ACTH remains unclear. In vitro experiments showed that blocking EGFR activity with gefitinib, an EGFR tyrosine kinase inhibitor, lead to attenuated proopiomelanocortin (POMC) expression in corticotrophs [28].

Kinase inhibitors appear as a promising alternative to manage ectopic Cushing's syndrome due to MTC and, eventually, due to other neuroendocrine tumors in whom surgery is not feasible, relegating bilateral adrenalectomy for unresponsive cases.

ANAPLASTIC THYROID CARCINOMA

Anaplastic thyroid carcinoma is a rare but highly aggressive malignancy. At presentation is often surgically unresectable due to invasion of surrounding structures. Furthermore is refractory to conventional therapies including chemotherapy, radiotherapy and radioiodine therapy. As a consequence, the median overall survival is about six months.

Molecular genetics of ATCs is still in part unknown. The efficacy of imatinib in a phase II study was tested in 11 patients with ATC because of the overexpression and overactivation of c-Kit and PDGFR. Among eight evaluable for response, two had a partial response and four stable disease [29].

BRAFV600E mutation was demonstrated in about 30% of ATCs and was exploited as potential therapeutic target. A phase II study with sorafenib, enrolling 20 patients was therefore designed; two patients had a partial response and five stable disease with an overall median progression free survival of 1.9 months [30]. Sorafenib seems to have activity in ATC but at a low frequency.

A dramatic response to vemurafenib was observed in a single patient with BRAF-mutated anaplastic thyroid cancer [31]. Vemurafenib is a B-Raf enzyme inhibitor approved for adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma.

There is still a major unmet need for effective treatments in patients with anaplastic thyroid carcinoma.

Keywords: Anaplastic thyroid carcinoma, Cushing's syndrome, Differentiated thyroid carcinoma, Medullary thyroid carcinoma, Thyroid carcinoma

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Authors declare no conflict of interest.

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