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Complications of Treatment

Management of treatment-related toxicities in advanced medullary thyroid cancer

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ABSTRACT

Progress in the treatment of advanced medullary thyroid cancer (MTC) has resulted from the approval of 2 drugs within the past 5 years, vandetanib and cabozantinib. These multikinase inhibitors (MKIs) possess overlapping specificities for multiple kinase targets implicated in the progression of MTC. Both drugs are associated with toxicities, including hypertension, hemorrhage/perforation, diarrhea and other gastrointestinal events, several dermatologic events, and hypothyroidism. In addition, vandetanib is uniquely associated with QTc prolongation through interaction with myocardial potassium channels, and cabozantinib is uniquely associated with hand-foot skin reaction. Treatment-related toxicities occur frequently and can be severe or life-threatening, and patients undergoing long-term treatment will likely experience adverse events (AEs). Here we offer specific practical recommendations for managing AEs commonly occurring with vandetanib and cabozantinib. The recommended approach relies on early recognition and palliation of symptoms, dose interruption, and dose reduction as necessary in order for the patient to maintain the highest tolerable dose for as long as possible and optimal quality of life. Treatment guidelines do not specify a recommended sequence for treating with vandetanib and cabozantinib; however, most patients will receive both drugs during their lifetime. The choice for first-line therapy is individualized after a risk-benefit assessment and depends on physician preference and patient-related factors, such as comorbid conditions. Because most generalist practices may not be familiar with the intricacies of agents such as vandetanib and cabozantinib, we commend that patients with advanced MTC be managed and treated by a thyroid cancer specialist with coordination of care within a multidisciplinary team.

Introduction

Medullary thyroid cancer (MTC) is a rare neuroendocrine malignancy that arises in the calcitonin-producing parafollicular cells (C cells) of the thyroid [1,2]. A calcitonin level of > 1000 pg/mL suggests the presence of advanced disease with distant metastasis, generally occurring in the liver, lung, bone, lymph nodes, and brain [1–3]. Because of its rarity, the exact prevalence of advanced MTC is not known; however, its incidence is estimated to be approximately 0.2 per 100,000 population [4]. Because 20% of cases of MTC are associated with multiple endocrine neoplasia syndrome, all patients with MTC should be screened for germline mutations in the rearranged during transfection (RET) proto-oncogene [5]. The 5-year survival rate of early-stage (Stages I-III) disease is > 90% but only < 30% in advanced MTC [1]. Similarly, although surgery is potentially curative in early-stage MTC, advanced MTC is not curable by surgery or currently available therapies, defining a high unmet need in this patient population [1,2].

Multikinase inhibitors in the treatment of advanced medullary thyroid cancer

Although treatment with multikinase inhibitors (MKIs) is not curative, they do have a role in treating advanced/metastatic MTC that is symptomatic, progressive, and life-threatening. Two such inhibitors, vandetanib (Caprelsa®; Sanofi Genzyme, Cambridge, MA) and cabozantinib (Cometriq®; Exelixis, South San Francisco, CA) target multiple

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Table 1
Selected efficacy and safety results in the multinational, pivotal, phase III trials of vandetanib and cabozantinib in advanced medullary thyroid cancer [7,8]. (*Note*. Data do not provide direct comparisons due to differences in study design and patient populations.)

Parameter	Vandetanib—ZETA trial	Cabozantinib—EXAM trial
Median PFS vs placebo	Not reached (vs 19.3 mo)	11.2 mo (vs 4.0 mo)
HR (95% CI)	0.46 (0.31–0.69)	0.28 (0.19–0.40)
P-value	< 0.001	< 0.001
ORR by RECIST	45%	28%
OR (95% CI)	5.48 (2.99–10.79)	(OR not given)
P-value	< 0.001	< 0.001
Disease control	87%	94%
OR (95% CI)	2.64 (1.48–4.69)	(OR not given)
P-value	0.001	
Biochemical response Calcitonin level	69% of patients OR, 72.9 (26.2–303.2)	−45%, mean +57% (mean, placebo)
P-value	< 0.001	< 0.001
Biochemical response CEA level	52% of patients OR, 52.0 (16.0–320.3)	−24%, mean +89% (mean, placebo)
P-value	< 0.001	< 0.001
AEs (all grades) in ≥30% of patients	Diarrhea, rash, nausea, hypertension	Diarrhea, PPE, decreased appetite, decreased weight, nausea, fatigue
Discontinuations for AEs	12%	16%
Dose reductions for AEs	35%	79%

AE, adverse event; CEA, carcinoembryonic antigen; CI, confidence interval; EXAM, Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer; HR, hazard ratio; OR, odds ratio; ORR, objective response rate (all partial responses); PFS, progression-free survival; PPE, palmar-plantar erythrodysesthesia; RECIST, Response Evaluation Criteria in Solid Tumors; ZETA, Zactima Efficacy in Thyroid Cancer Assessment.

kinases and are recommended in published clinical guidelines for MTC [1,2,6,7]. Additionally, both vandetanib and cabozantinib were approved based on results of pivotal phase III trials in MTC [6,7]. Importantly, because these 2 trials enrolled different patient populations and differed as to whether patients receiving placebo were allowed to cross over upon disease progression, the results (Table 1) cannot be directly compared but are provided only as summary information [8,9]. For example, the difference in median progression-free survival (PFS) in these studies, best seen in the placebo arm, reflects a key difference in trial eligibility: the cabozantinib EXAM study required radiographically documented disease progression at enrollment, which resulted in a sicker patient population with a placebo PFS of 4.0 months, whereas the vandetanib ZETA study did not require radiographic progression and as a result the placebo arm had a PFS of 19.3 months [8,9]. Furthermore, crossover from placebo to vandetanib was allowed, confounding the assessment of overall survival; the cabozantinib trial did not permit crossover, potentially allowing for credible assessments of the effects on overall survival [8,9].

The basis for multikinase inhibitor–associated toxicity

Vandetanib and cabozantinib are broad-spectrum MKIs with largely overlapping kinase selectivities [6,7]. These drugs primarily target vascular endothelial growth factor receptors (VEGFRs) but also target many tyrosine kinases implicated in modifying MTC disease pathogenesis, including mutated RET [6,7]. The efficacy and toxicities of MKIs overlap and likely reflect target-binding affinities specific to each drug. The kinase targets of vandetanib include VEGFR, RET, members of the epidermal growth factor receptor (EGFR) family, BRK), TIE2, and members of the ephrin receptor and SRC nonreceptor kinase families [6]. In preclinical models, vandetanib reduced tumor-induced angiogenesis and tumor vessel permeability, and inhibited tumor growth and metastasis [6].

Cabozantinib shares some of these targets, including VEGFR family members, RET, and TIE2, and also targets MET, KIT, TRKB, FLT3, AXL, TYRO3, and ROS1 tyrosine kinases, among others [7]. Preclinical studies demonstrated that cabozantinib inhibits angiogenesis; disrupts tumor vasculature; inhibits tumor cell migration, invasion, and proliferation; and promotes tumor cell death [7,10].

Treating advanced medullary thyroid cancer: who we treat and why

Care is needed in identifying patients with advanced MTC who are candidates to receive MKIs. The patient population studied in the phase III trial of vandetanib was composed of adults with measurable, unresectable, locally advanced or metastatic MTC (hereditary or sporadic) whose disease was confirmed by tumor analysis or the presence of a germline RET mutation; tumor progression was not required for enrollment. Patients were required to have a serum calcitonin level of ≥500 pg/mL. Patients with significant cardiac, hematopoietic, hepatic, or renal dysfunction were excluded. Prior systemic therapy for MTC (including chemotherapy or other MKIs) was allowed [9]. The population enrolled in the phase III cabozantinib trial was similar in most respects and included adults with histologically confirmed, unresectable, locally advanced or metastatic MTC. However, in contrast to the vandetanib trial, documented radiographic disease progression during the prior 14 months was required for the cabozantinib trial [8].

The use of MKIs is recommended conditionally in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (Category 1 recommendation) and treatment guidelines of the American Thyroid Association (Grade A recommendation). These guidelines indicate that patients' disease should be symptomatic or progressing before initiating treatment; increasing levels of tumor markers alone are not sufficient criteria [1,2]. An active surveillance approach is generally recommended for patients with stable, slowly progressing, or indolent disease that is not symptomatic or likely to cause immediate symptoms or complications [1]. Therefore, a risk-benefit assessment should be performed for each patient with MTC to determine if and when to initiate MKI treatment [1,2,6].

Patient-specific factors to consider include overall disease burden, locations and pace of disease progression, patient age and comorbid conditions (e.g., preexisting QTc prolongation or hepatic impairment), and importantly, patient preference. Because treatment guidelines do not have a recommended sequence for treating with MKIs, the choice of agent—vandetanib or cabozantinib—is individualized [1,2]. Indeed, most patients will receive both agents, administered separately, during their lifetime, and therefore, the preference for first-line agent varies by physician and will depend on patient-related factors. Many patients in clinical practice are likely to have comorbid conditions that would have excluded them from clinical trials, which must be taken into account. In some cases these patients are more challenging to manage with respect to potential toxicities. The distinct pharmacokinetic properties and drug-drug interactions of vandetanib and cabozantinib are important to know for both choosing an initial therapy and managing toxicities (Table 2) [6,7].

Dosing considerations

Because patients may undergo long-term treatment with vandetanib and/or cabozantinib, most will experience MKI-associated adverse events (AEs) [8,9]. Therefore, providers need to have a strong understanding of how to manage AEs and a practice setting that will allow expeditious recognition of AEs in order to optimize management. The rationale for early recognition and optimal management of AEs is to improve tolerance and adherence to the treatment regimen, while mitigating potential risks, in an effort to optimize clinical outcomes and afford patients an acceptable quality of life [11]. The general management approach relies first upon palliation of symptoms where