Medullary thyroid cancer: advances in treatment and management of common adverse events associated with therapy

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Thyroid cancer is the most common malignancy of the endocrine system. Medullary thyroid cancer (MTC), an intermediate differentiated histotype of thyroid cancer, accounts for approximately 4% of all thyroid cancer cases in the United States. MTC tumors are characterized by increased activation of the proto-oncogene *RET*, which encodes a receptor tyrosine kinase that promotes cell growth, differentiation, and survival. *RET* mutations are present in almost all patients with hereditary MTC and in up to 50% of patients with sporadic MTC. MTC tumors also are characterized by overexpression of vascular endothelial growth factor receptors. Until recently, systemic therapy options for MTC treatment were limited. However, based on promising efficacy demonstrated in other solid tumor types, many oral tyrosine kinase inhibitors are being investigated for the treatment of patients with MTC. Recently, vandetanib was approved in the United States for the treatment of patients with symptomatic or progressive MTC with locally advanced or metastatic disease. Common adverse events associated with tyrosine kinase inhibitors under investigation for MTC include diarrhea, rash, hypertension, and QTc prolongation.

Thyroid cancer is the most common malignancy of the endocrine system in the United States. In 2011, an estimated 48,020 individuals were diagnosed with thyroid cancer, and an estimated 1,740 individuals died from the disease.[1] About 76% of the estimated new diagnoses are in women, making thyroid cancer the fifth most common cancer in women.[1] According to data from the Surveillance Epidemiology and End Results (SEER) registry, the 5-year relative survival rate from 1999 to 2006 for all stages of thyroid cancer was 97.3%, yet in patients with metastatic disease, it was only 58.1%.[2]

Thyroid cancer has 3 main histotypes: differentiated, which consists of papillary, follicular, and Hürthle cell carcinoma; medullary, which has intermediate differentiation; and anaplastic, which is undifferentiated.[3] Most thyroid cancers (94%) are classified as differentiated and are derived from the follicular cells. Anaplastic thyroid cancer, which accounts for 2% of all cases, is the most aggressive and lethal form of the disease, and is also derived from the follicular cells. In contrast, medullary thyroid cancer (MTC; 4% of all cases) is derived from the parafollicular cells (C cells) and is characterized by hypersecretion of calcitonin.[3,4]

In about 25% of patients, MTC results from an autosomal dominant germline mutation. Hereditary MTC may take the form of multiple endocrine neoplasia type 2A (MEN 2A), consisting of MTC, pheochromocytoma, and primary hyperparathyroidism; MEN type 2B (MEN 2B), consisting of MTC, pheochromocytoma, and developmental abnormalities; or familial MTC (FMTC), a variant of MEN 2A consisting of MTC with no other endocrinopathies.[3,5,6] In the remaining 75% of patients, the disease is sporadic.[5,7] Mutations in the proto-oncogene *RET* (rearranged during transfection) are found in almost all patients who have hereditary MTC, and in up to 50% of patients with sporadic MTC.[7] *RET* encodes a transmembrane receptor tyrosine kinase that has key roles in cell growth, differentiation, and survival.[6] In MTC, gain-of-function mutations in *RET* result in constitutive activation of the RET receptor, leading to dysregulation of these processes.[6] In addition, these highly vascularized tumors have been shown to overexpress vascular endothelial growth factor receptors (VEGFRs), which are transmembrane receptor tyrosine kinases that stimulate endothelial cell

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proliferation, migration, and survival; MTC tumors also have been shown to overexpress VEGF.[8]

Because the incidence of MTC is relatively low, there have been few randomized clinical trials of systemic therapies in patients with MTC. However, insight on the gene- and protein-expression profiles of MTC tumors has led to potentially significant advances in the treatment paradigm. Small-molecule therapies that are targeted to inhibit signal transduction by the receptor tyrosine kinases involved in cell proliferation, angiogenesis, and apoptosis (including VEGFRs, platelet-derived growth factor receptors [PDGFRs], stem cell factor receptor [c-KIT], and *RET*) are successfully used for treating patients who have solid tumors that have been shown to overexpress VEGF and are likely dependent on angiogenesis to drive tumor growth and progression.[9] Such tumors include renal cell carcinoma (RCC), which is treated with sunitinib and sorafenib; hepatocellular carcinoma (HCC), treated with sorafenib; gastrointestinal stromal tumors (GIST), treated with sunitinib; and pancreatic neuroendocrine tumors, treated with sunitinib.[10,11] On the basis of the success of these treatments in these tumor types, researchers have recently investigated the use of tyrosine kinase inhibitors (TKIs) for the treatment of patients with MTC, with a particular focus on inhibition of *RET* signaling and VEGFR.[3] This article will review the clinical study results of TKI treatment in patients with advanced MTC, the common adverse events (AEs) associated with these therapies, and methods for the successful management of these AEs.

Diagnosis and current treatment

Patients with hereditary MTC typically are diagnosed via genetic testing before the development of macroscopic disease.[4] In the MTC management guidelines of the American Thyroid Association (ATA), recommendations include germline *RET* testing for patients with a family history of MEN 2 or FMTC and a risk of autosomal dominant inheritance.[5] If testing identifies MEN 2A, then serum levels of intact parathyroid hormone and calcium are measured. Patients with MEN 2A usually show symptoms of MTC before symptoms of pheochromocytoma or hyperparathyroidism. If testing identifies MEN 2B, which is a more aggressive form of MEN 2 that develops earlier in life than does MEN 2A, then the ATA recommends measurement of calcitonin levels, a cervical ultrasound, and prophylactic thyroidectomy.[5] Gastrointestinal manifestations (including vomiting, dehydration, failure to thrive, and possible intestinal obstruction) often are the initial presenting symptoms in patients with MEN 2B.[5] MEN 2B also is characterized by the presence of developmental defects, including musculoskeletal abnormalities; neuromas of the lips, tongue, and conjunctiva; medullated corneal nerve fibers; and intestinal and urinary ganglioneuromatoses.[5]

Patients with sporadic disease often present with an asymptomatic nodule located in an upper pole of the thyroid.[3,4,12] Because of the high levels of calcitonin secreted in patients with advanced MTC, as well as the secretion of adrenocorticotrophic hormone and calcitonin gene–related peptide in some patients, the presenting symptoms may include pruritus, flushing, Cushing's syndrome, and diarrhea. Other symptoms include cervical lymphadenopathy, upper aerodigestive tract pressure symptoms, hoarseness, and dysphagia.[3,12] Metastatic disease also may be accompanied by chest pain, dyspnea, bone pain, and neurologic abnormalities.[13] Serum levels of calcitonin and carcinoembryonic antigen (CEA) are used as markers for diagnosis, and findings are confirmed by imaging studies (magnetic resonance imaging, positron-emission tomography/computed tomography, ultrasound) and biopsy.[3,4,14]

Surgery (typically total thyroidectomy with or without bilateral central neck dissection) is the main treatment for MTC.[3] An analysis of data from 1,252 patients with MTC in the SEER registry found the 10-year survival rate after surgery to be about 76% in patients with regional disease and 40% in patients with metastatic disease.[15] The ATA management guidelines advise that cytotoxic chemotherapy should not be used as first-line therapy in patients with persistent or recurrent disease because of limited efficacy; external-beam radiation therapy has a limited role in patients with advanced MTC, and postoperative radioactive iodine is not effective because C cells do not take up iodine.[5] Taken together, the survival data and limited therapy options highlight the need for new approaches to the treatment of patients with MTC.

Recent advances in MTC

Targeted TKIs represent a novel approach to MTC treatment. Inhibition of *RET*, VEGFRs, and other molecules such as epidermal growth factor receptors, hepatocyte growth factor, PDGFRs, Raf, and c-KIT may impede MTC tumor growth and development. Several TKIs currently are under investigation in clinical trials of patients with MTC, including vandetanib, sunitinib, sorafenib, cabozantinib (XL184), motesanib, and axitinib. Of note, all agents under investigation are targeted against *RET* signaling, VEGFR, or both (Table 1).[16-25] Presently, vandetanib is the only approved therapy for MTC. It remains to be seen how the results of ongoing phase II and III trials of small-molecule TKIs will affect the treatment paradigm for MTC.

TABLE 1 Targets and mechanisms of action of targeted oral therapies that have been investigated for the treatment of patients with medullary thyroid cancer

Agent	Target(s)	Mechanism of action
Vandetanib[16-18]	*RET* VEGFR EGFR	Inhibits endothelial cell proliferation and migration Reduces tumor vessel permeability Inhibits tumor cell proliferation, migration, angiogenesis
Cabozantinib (XL184)[18,19]	MET VEGFR-2 *RET* proto-oncogene	Inhibits tumor growth and angiogenesis Mediates tumor regression
Sorafenib[18,20-22]	Raf VEGFR-2 VEGFR-3 PDGFR *RET*	Inhibits cell division and proliferation Inhibits tumor angiogenesis
Sunitinib[18,23]	*RET* VEGFR-2 PDGFR c-KIT	Inhibits angiogenesis and cell proliferation
Motesanib[18,24]	VEGFR-1 VEGFR-2 VEGFR-3 PDGF c-KIT	Inhibits angiogenesis and cell proliferation
Axitinib[18,25]	VEGFR-1 VEGFR-2 VEGFR-3	Inhibits angiogenesis

Abbreviations: EGFR, epidermal growth factor receptor; KIT, stem cell factor; MET, hepatocyte growth factor; PDGFR, platelet-derived growth factor receptor; *RET*, rearranged during transfection; VEGFR, vascular endothelial growth factor receptor.

The efficacy and tolerability of vandetanib (100 mg and 300 mg daily),[26,27] sunitinib (50 mg, with a 4 weeks on/2 weeks off schedule),[23] sorafenib (800 mg daily),[28] and motesanib (125 mg daily)[29] were studied in phase II clinical trials that included only patients with advanced MTC. Axitinib was evaluated in a phase II study of 60 patients with advanced thyroid cancers that included 12 patients with MTC.[25] Cabozantinib was analyzed in a phase I dose-escalation study of 85 patients that included 37 patients with advanced MTC.[19] All of the therapies studied demonstrated promising efficacy and were generally well tolerated (Table 2).

To date, vandetanib is the only agent to be evaluated in a phase III trial of patients with MTC.[27] The ZETA trial was an international, randomized, double-blind trial that evaluated outcomes in 331 patients with MTC that was locally advanced or metastatic, hereditary or sporadic. The patients were randomized 2:1 to receive vandetanib 300 mg/day (n = 231) or placebo (n = 100) until disease progression. The primary end point was progression-free survival (PFS), and the secondary end points were the objective response rate (ORR); the disease control rate at 24 weeks; duration of response; overall survival (OS); biochemical response; time to worsening of pain; safety; and tolerability.[27]

Vandetanib demonstrated therapeutic efficacy on all evaluable efficacy end points in ZETA. At a median follow-up of 24 months, median PFS was not reached with vandetanib and was 19.3 months with placebo (hazard ratio [HR], 0.46; 95% confidence interval [CI]: 0.31-0.69; $P < .001$).[30] The ORRs for vandetanib and placebo were 44% and 1%, respectively.[30] OS data were immature at the data cut-off (HR, 0.89; 95% CI: 0.48-1.65).[27] Biochemical response—with complete response defined as a normalization of serum levels, and partial response defined as ≥ 50% decrease from baseline in serum calcitonin and CEA for ≥ 4 weeks—was 69% and 52%, respectively, with vandetanib, compared with 3% and 2% with placebo for calcitonin (odds ratio [OR], 72.9; 95% CI: 26.2-303.2; $P < .001$), and CEA (OR, 52.0; 95% CI: 16.0-320.3; $P < .001$).[27]

The most common AEs in ZETA (vandetanib vs placebo) were diarrhea or colitis (56% and 26%, respectively), rash (45% and 11%), nausea (33% and 16%), hypertension (32% and 5%), and headache (26% and 9%). The most common grade 3 (severe) or 4 (life-threatening) AEs were diarrhea (11% and 2%), hypertension (9% and 0%), prolonged QT interval (8% and 1%), and fatigue (6% and 1%).[30] More vandetanib-treated patients discontin-

TABLE 2 Completed clinical trials of targeted oral therapies for the treatment of patients with medullary thyroid cancer

Agent	Study design	N	Tumor response	Biochemical response[a]	Median TTP/ PFS (mo)	Grade 3/4 AEs (≥ 5%)
Vandetanib	Open-label, single-arm study of vandetanib 100 mg/ day in locally advanced or metastatic MTC[26]	19	16% (3/19) PR; 53% (10/19) SD ≥ 24 wk	• 16% (3/19) ↓ calcitonin • 5% (1/19) ↓ CEA	NR	Muscular weakness, hypertension, myalgia, phaeochromocytoma, QTc prolongation, diplopia, visual disturbance, diabetes insipidus (5% each)
	Open-label, single-arm, phase II study of vandetanib 300 mg/day in unresectable, locally advanced or metastatic hereditary MTC[27]	30	20% (6/30) PR; 53% (16/30) SD ≥ 24 wks	• 80% (24/30) ↓ calcitonin • 53% (16/30) ↓ CEA	PFS, 27.9	QTc prolongation (20%), diarrhea (10%), nausea (10%), hypertension (10%), fatigue (7%), vomiting (7%)
	Randomized, double-blind, placebo-controlled study of vandetanib 300 mg/day in unresectable, locally advanced or metastatic MTC[27]	331 (n = 231, vandetanib)	ORR 45% DCR 87%	• 69% ↓ calcitonin • 52% ↓ CEA	PFS not reached	Diarrhea (11%), hypertension (9%), QTc prolongation (8%), fatigue (6%)
Cabozantinib (XL184)	Phase I dose-escalation study in patients with advanced malignancies[19]	85[b]	29% (10/35) PR; 41% (15/37) SD ≥ 6 mos	• Range of 3%-99% ↓ calcitonin in 28 of 30 patients with measurable disease • Range of 13%-94% ↓ CEA in 24 of 28 patients with CEA data and measurable disease	NR	Fatigue (10%), HFS (10%), increased lipase (10%), diarrhea (7%), decreased weight (6%), increased amylase (5%)
Sorafenib	Phase II trial of sorafenib 400 mg orally twice daily in locally advanced or metastatic MTC[28]	21[c]	6% (1/16) PR; 88% (14/16) SD (8 with SD ≥ 15 mo)	• 85% (17/20) ↓ calcitonin or CEA • 55% (11/20) ↓ calcitonin and CEA	PFS, 17.9	HFS (14%), hypertension (10%), diarrhea (10%), infections (10%), pulmonary embolism (5%), joint pain (5%), thrombocytopenia (5%)
Sunitinib	Phase II trial of sunitinib 50 mg (schedule, 4 weeks on/2 weeks off) in MTC with disease progression ≤ 6 mos and not amenable to surgery or radiotherapy[23]	25	35% (8/23) PR; 57% (13/23) SD	NR	TTP, 6.5[d]	Lymphopenia (25%), neutropenia (21%), HFS (17%), mucositis (13%)
Motesanib	Phase II study of motesanib 125 mg/day in progressive or symptomatic, advanced or metastatic MTC[29]	91	2% (2/91) PR; 81% (74/91) SD (48% had SD ≥ 24 wk)	• 83% (69/83) ↓ calcitonin • 75% (63/84) ↓ CEA	PFS, 11.1[d]	Diarrhea (13%), hypertension (10%), fatigue (8%)
Axitinib	Phase II study of axitinib 5 mg twice daily in advanced thyroid cancers[25]	60[e]	18% (2/11) PR; 27% (3/11) SD	NR	PFS, 18.1	Hypertension (12%), proteinuria (5%), fatigue (5%)

Abbreviations: AE, adverse event; CEA, carcinoembryonic antigen; DCR, disease control rate; HFS, hand-foot syndrome; mg, milligram; mo, month; MTC, medullary thyroid cancer; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PR, partial response; QTc, QT interval corrected for heart rate; SD, stable disease; TTP, time to progression
[a] Defined as a ≥ 50% decrease from baseline; [b] Thirty-seven patients had a diagnosis of advanced MTC; 35 were evaluable; [c] Study originally made up of 2 arms: arm A (familial MTC) and arm B (sporadic MTC). Arm A prematurely terminated due to slow accrual; [d] Reported value in weeks was converted to months by dividing by 4.34; [e] Eleven patients had a diagnosis of advanced MTC; all were evaluable.

ued treatment than did placebo patients (12% and 3%).[27] In addition, 35.9% (83/231) of vandetanib-treated patients required a dose reduction because of AEs; of those, 81 (35.1%) had their dose reduced to 200 mg daily, and 2 (0.9%) had their dose reduced directly to 100 mg daily (AstraZeneca, ZETA trial data on file). A total of 30 patients (13.1%) who were dose reduced to 200 mg daily required a subsequent dose reduction; of those, 29 (12.6%) were dose reduced directly to 100 mg daily, and 1 (0.4%) was dose reduced to 200 mg every other day before receiving 100 mg daily (AstraZeneca, ZETA trial data on file). The AE profile of vandetanib in patients with MTC, as observed in ZETA, was consistent with that observed in phase II trials of vandetanib in patients with other tumor types.[31]

Based on the results of ZETA, the Food and Drug Administration (FDA) approved vandetanib for the treatment of symptomatic or progressive MTC in patients

TABLE 3 National cancer institute common terminology criteria for adverse events (v3.0) grading severity of common adverse events associated with tyrosine kinase inhibitor therapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of < 4 stools/day over baseline; mild increase in ostomy output vs baseline	Increase of 4-6 stools/day over baseline; intravenous fluids indicated < 24 h; moderate increase in ostomy output vs baseline, not interfering with ADL	Increase of ≥ 7 stools/day over baseline; incontinence; intravenous fluids ≥ 24 h; hospitalization; severe increase in ostomy output vs baseline interfering with ADL	Life-threatening consequences (eg, hemodynamic collapse)	Death
Rash/ desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of BSA	Severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Hypertension	Asymptomatic, transient (< 24 h) increase by > 20 mm Hg (diastolic) or to > 150/100 if previously WNL; intervention not indicated	Recurrent or persistent (≥ 24 h) or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated	Requiring more than 1 drug or more intensive therapy than previously	Life-threatening consequences (eg, hypertensive crisis)	Death
Prolonged QTc interval	QTc > 0.45-0.47 s	QTc > 0.47-0.50 s; ≥ 0.06 s above baseline	QTc > 0.50 s	QTc > 0.50 s; life-threatening signs or symptoms (eg, arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death

Abbreviations: ADL, activities of daily living; BSA, body surface area; CHF, congestive heart failure; h, hour(s); mm Hg, millimeter of mercury (unit of pressure); QTc, QT interval corrected for heart rate; s, second(s); WNL, within normal limits.

with unresectable locally advanced or metastatic disease. The use of vandetanib in patients with indolent, asymptomatic, or slowly progressing disease should be carefully considered because of the treatment-related risks associated with therapy.[30] The European Union's European Medicines Agency is considering vandetanib for the treatment of MTC.

Management of common AEs

The TKIs in development for MTC are orally administered, and patient management strategies differ from those for intravenously administered anticancer agents, which require regular visits to a health care provider for drug administration. Educating patients by reviewing measures to prevent or minimize side effects and promoting early recognition and prompt reporting of side effects are important steps for optimizing adherence to therapy and, ultimately, patient outcomes. Oncology nurses are in an ideal position to provide individualized patient education and support during orally administered cancer therapy.[32] Oncology nurses also can help patients and caregivers learn to distinguish symptoms that can be self-managed from those that require medical attention.[32]

Pivotal studies of TKIs in a variety of solid tumors have demonstrated that these agents have shared and manageable AEs. For example, in patients with advanced RCC, sorafenib was associated with diarrhea, rash or desquamation, hand-foot skin reactions, alopecia, and fatigue (all > 20%).[33] In patients with HCC, sorafenib-associated AEs included diarrhea, fatigue, and hand-foot skin reactions (all ≥ 20%).[34] Similarly, the administration of sunitinib to patients with advanced RCC was associated with diarrhea, fatigue, nausea, stomatitis, vomiting, hypertension, hand-foot, syndrome, and mucosal inflammation (all ≥ 20%).[35] Patients with GIST experienced diarrhea, anorexia, skin discoloration, mucositis or stomatitis, asthenia, altered taste, and constipation with sunitinib treatment (all ≥ 20%).[11]

The remainder of this review focuses on management strategies for AEs—including diarrhea, rash, hypertension, and prolonged QTc interval—that are shared among the targeted therapies under investigation for MTC. We used the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) to grade the severity of these AEs in the clinical studies of TKIs in patients with MTC (Table 3). [36] It should be noted that an updated version of these grading criteria is now available.[37] We review the suggested management strategies used in the ZETA trial (Table 4) and in the approved prescribing information for vandetanib,

TABLE 4 Management strategies and dose reductions used in the ZETA trial for selected vandetanib-related adverse events

Toxicity	Severity[a]	Recommendations
Diarrhea	Grade 1/2	Treated with standard medications Electrolyte supplementation with regular laboratory monitoring Dose modifications not allowed
	Grade 3/4	Vandetanib withheld until toxicity resolved to grade 1 or baseline, then dose permanently reduced to 200 mg If toxicity recurred, dose reduced to 100 mg upon resolution If severe toxicity recurred after dose reduction to 100 mg, vandetanib permanently discontinued
Rash	Grade 1/2	Treated with standard medications (mild- to moderate-strength steroid creams, either topical or systemic antibiotics, topical or systemic antihistamines, and retinoid creams) Dose modification not necessary
	Grade 3/4	Vandetanib withheld until toxicity resolved to grade 1 or baseline, then dose permanently reduced to 200 mg If toxicity recurred, dose reduced to 100 mg on resolution If severe toxicity recurred after dose reduction to 100 mg, vandetanib permanently discontinued
Hypertension	Grade 3	Vandetanib continued if BP was controlled with increased antihypertensive medication If BP could not be stabilized with increased antihypertensive medication, vandetanib withheld until BP was controlled to baseline level[b]
	Grade 4	Vandetanib withheld until blood pressure was controlled to baseline level[b]
QTc prolongation	QTc value $\geq$ 500 ms and $<$ 550 ms or prolonged $\geq$ 60 ms and $<$ 100 ms from baseline	Dosing continued; ECG repeated (in triplicate) within 48 hours; if the repeat ECG did not meet criteria, patient could continue vandetanib If repeat ECG met criteria, vandetanib withheld until QTc recovered to $<$ 480 ms or baseline, then dose reduced to 200 mg initially[c] If toxicity recurred, dose reduced to 100 mg on resolution
	QTc value $\geq$ 550 ms or prolonged $\geq$ 100 ms from baseline	ECGs and electrolytes should be performed 3 times a week to monitor QTc Vandetanib withheld until QTc recovers to $<$ 480 ms or baseline, then dose reduced to 200 mg/day[c] If toxicity recurred, dose reduced to 100 mg on resolution

Abbreviations: BP, blood pressure; ECG, electrocardiogram; mg, milligram; ms, millisecond; QTc, QT interval corrected for heart rate.
[a] As defined by Common Terminology Criteria for Adverse Events (CTCAE v3.0); [b] If vandetanib was stopped for any reason in patients with increased blood pressure as a result of therapy and patient required blood pressure management with pharmacotherapy, blood pressure medication should be managed appropriately; [c] After QTc prolongation has resolved, ECGs should be performed at 1, 2, 4, 8, and 12 weeks, and every 12 weeks thereafter, once vandetanib is restarted.

as well as those used for targeted therapies in other solid tumors for these 4 AEs. These management strategies may be useful for the management of AEs associated with TKIs that are in development for MTC.

Diarrhea

Diarrhea is a common presenting symptom of MTC due to increased calcitonin, and it is important to distinguish whether it is a manifestation of disease progression or is related to the treatment. Thus, prompt reporting of diarrhea by the patient to the health care provider is necessary to avoid worsening severity of symptoms and/or discontinuation of therapy. According to the ATA guidelines for MTC, first-line treatments for diarrhea are loperamide or codeine.[5] Additional management strategies that have been used with other TKIs in other solid tumors include an increased intake of fluid, dietary modifications (ie, consumption of bland foods), and administration of probiotics,[38,39] as well as hospitalization and administration of octreotide and antibiotics for more severe cases.[40,41]

With the suggested management strategies and dose reductions used in ZETA (Table 4), the incidence of vandetanib dose reduction for grade 3 or 4 diarrhea was

2.2% (5/231 patients) to vandetanib 200 mg, and 1.7% (4/231 patients) to vandetanib 100 mg [AstraZeneca, ZETA trial data on file]. Two patients discontinued vandetanib because of diarrhea [AstraZeneca, ZETA trial data on file]. According to the prescribing information for vandetanib, routine antidiarrheal agents are recommended should diarrhea develop during therapy. Because diarrhea may cause electrolyte imbalances, serum electrolytes and electrocardiograms (ECGs) should be carefully monitored in patients with diarrhea. If severe diarrhea (grade 3 or higher) develops, vandetanib should be discontinued until diarrhea improves to grade 1. Upon improvement, vandetanib may be resumed at a reduced dose.[30]

Rash

As with diarrhea, it is important to educate patients on the importance of prompt reporting when grade 1/2 rash develops to avoid worsening severity of symptoms and/or discontinuation of therapy. Because sun exposure can be a major trigger of rash development in some patients, the importance of prophylactic use of moisturizing cream with a sun protection factor must be stressed. Modifying outdoor routines to minimize sun exposure can minimize rash and make treatment more tolerable. In addition, to prevent splitting of the skin at the tips of the fingers, patients should moisturize their hands and wear gloves when doing dishes or yard work. Patients may use a liquid bandage on painful skin splits on their fingers.

Management strategies for rash that have been used with TKIs in a range of solid tumor malignancies include topical or systemic antibiotics, steroid creams, systemic antihistamines, and retinoid creams.[42-45] Dose reduction or treatment interruption has been recommended for grade 3 or 4 reactions, or for grade 2 reactions that are particularly distressing and affect patient quality of life.[44] Similar management strategies were used in ZETA (Table 4). In addition, patients were counseled to follow a program of moisturizing the skin and using sun-protective measures while they received vandetanib to reduce the risk and severity of skin rash. Immediate symptomatic treatment was provided to patients with grade 2 events. Dose reduction was needed if grade 3/4 rash developed during ZETA (Table 4); the incidence of this was 2.6% (6/231 patients) to vandetanib 200 mg, and 0.9% (2/231 patients) to vandetanib 100 mg [AstraZeneca, ZETA trial data on file]. In all, 4 patients discontinued vandetanib because of skin reactions [AstraZeneca, ZETA trial data on file]. In addition to the strategies above, the vandetanib prescribing information suggests systemic corticosteroids and advises patients to wear sunscreen and sun-protective clothing for 4 months after discontinuation of therapy due to the 19-day half-life of vandetanib.[30]

Hypertension

Because hypertension may not be readily apparent in the office setting, nurses may encourage patients to self-monitor blood pressure and record their readings in a diary or journal. In addition, based on clinical experience with VEGFR inhibitors across tumor types, consensus recommendations suggest that a formal risk assessment of potential cardiovascular complications be conducted before the administration of any TKI that inhibits the VEGF signaling pathway.[46] This includes collecting a minimum of 2 standardized blood pressure measurements as well as doing a thorough patient history, physical examination, and laboratory evaluation to determine specific cardiovascular risk factors. The target blood pressure in patients who receive these therapies is $< 140/90$ mm Hg; however, the target blood pressure may be lower for patients with preexisting cardiovascular risk factors (eg, diabetes, chronic kidney disease). Efforts should be made to reach individual patient goals before anti-VEGF signaling pathway therapy is initiated.[46] The proper selection of an antihypertensive agent is critical, as some antihypertensives may result in potential drug interactions. For example, beta-blockers and thiazide diuretics should be avoided in combination with multitargeted TKIs, as they may prolong the QT interval.[46]

Antihypertensive therapy has been recommended for the management of hypertension associated with use of sunitinib in other tumor types. In addition, temporary sunitinib dose reductions or discontinuations have been recommended until blood pressure can be controlled.[38,47] In ZETA, patients who developed grade 3 hypertension could continue vandetanib if their blood pressure was controlled with increased antihypertensive medication. If it could not be stabilized in that way, or if the patient experienced grade 4 hypertension, then vandetanib was withheld until blood pressure returned to baseline. If vandetanib was stopped for any reason in patients whose blood pressure increased as a result of therapy, then blood pressure medication was appropriately managed (Table 4). In all, 3 patients reduced their vandetanib dose because of hypertension, and 2 patients discontinued vandetanib [AstraZeneca, ZETA trial data on file]. Routine monitoring of blood pressure is recommended, according to the approved prescribing information for vandetanib. Should the patient develop hypertension while on therapy, then treatment measures include antihypertensive medication or vandetanib dose reduction and/or interruption. If hypertension cannot be controlled with these strategies, vandetanib should not be restarted.[30]

Prolonged QT interval

The QT interval represents the duration of ventricle depolarization and subsequent repolarization on an ECG. Delays in repolarization may lead to the development of cardiac arrhythmias such as torsades de pointes (TdP), which may lead to sudden death. Multitargeted TKIs have demonstrated QT prolongation effects in patients with other solid tumors.[48,49] Thus far, it has not been observed in clinical studies of cabozantinib,[19] sorafenib,[28] or sunitinib[23] in patients with MTC, and has been reported in clinical studies of vandetanib (Table 2).[26,27]

To adjust for the relationship between heart rate and QT interval, Bazett's or Fridericia's formulas are used to determine a corrected QT interval (QTc).[50] With recommendations for dose reductions used to manage QTc prolongations (Bazett's formula) during ZETA (Table 4), the incidence of vandetanib dose reduction for QTc prolongation was 6.9% (16/231 patients) to vandetanib 200 mg, and 3.5% (8/231 patients) to vandetanib 100 mg [AstraZeneca, ZETA trial data on file]. Two patients discontinued vandetanib because of QT prolongation [AstraZeneca, ZETA trial data on file].

Using Fridericia's correction (QTcF), the prescribing information reports that 69% of patients who were treated with vandetanib in ZETA had QTc prolongation > 450 milliseconds, and 7% had QTc prolongation > 500 milliseconds. The mean QTcF change from baseline (ΔQTcF) was 35 milliseconds, and mean ΔQTcF remained above 30 milliseconds for the duration of ZETA (up to 2 years) in patients who received vandetanib. Overall, a total of 36% of vandetanib-treated patients experienced a > 60-millisecond increase in ΔQTcF.[30]

Prescribers and pharmacies that are certified with the vandetanib REMS (Risk Evaluation and Mitigation Strategy) program can prescribe and dispense vandetanib.[51] Nurses can play a critical role in identifying appropriate patients for vandetanib therapy and should be aware of patient selection guidelines. Vandetanib can be initiated in patients whose QTcF interval is ≤ 450 milliseconds, but not in patients with a history of TdP, congenital long-QT syndrome, bradyarrhythmias, or uncompensated heart failure.[30] In addition, because vandetanib can prolong QT interval in a concentration-dependent manner, the starting dose in patients with moderate (defined as creatinine clearance ≥ 30 mL/min to < 50 mL/min) and severe (defined as creatinine clearance < 30 mL/min) renal impairment should be reduced to a dose of 200 mg.[30] Although there are limited clinical data, the US prescribing information allows patients with severe renal insufficiency to receive vandetanib with a dose reduction to 200 mg based on pharmacokinetic data.[30] Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.[30]

Before patients begin vandetanib therapy, it is recommended that an ECG and levels of serum potassium, calcium, magnesium, and thyroid-stimulating hormone be obtained at baseline, at 2-4 weeks, at 8-12 weeks after they start therapy, and every 3 months thereafter. Electrolytes and ECGs may require more frequent monitoring if diarrhea is present. In the event of a QTc > 500 milliseconds, vandetanib dosing should be discontinued until the QTc returns to < 450 milliseconds, then dosing should be resumed at a reduced dose. Following any dose reduction for QT prolongation or any dose interruptions > 2 weeks, QT assessments should be conducted as previously described. The QT interval should be monitored closely in patients with renal impairment. Serum potassium levels should be maintained at 4 mEq/L or higher (within normal range), and serum magnesium and serum calcium should be kept within normal range.[51]

In addition to appropriate monitoring, drug therapies that prolong the QT interval or are associated with TdP should be avoided in combination with vandetanib.[51] A comprehensive list of such agents can be found on the Arizona Center for Education and Research on Therapeutics Web site.[52] If no alternative therapy exists and concomitant treatment with a drug that is known to prolong the QT interval is necessary, then more-frequent ECG monitoring should be performed.[51] It also may be helpful to give patients a list of "drugs to avoid" that they can present to their other health care providers.

Conclusion

In addition to vandetanib, several targeted therapies are in clinical development for the treatment of patients with advanced MTC. Common AEs associated with TKI therapy in patients with MTC include diarrhea, rash, hypertension, and prolonged QTc interval. Oncology nurses are at the forefront of educating patients about what to expect with these new medications and evaluating new ways to assist patients in controlling the AEs of therapy. Effective, timely, individualized management of TKI treatment–related AEs is essential to maximize both adherence to treatment and clinical outcomes in patients with advanced MTC.

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