

Vandetanib in Advanced Medullary Thyroid Cancer: Review of Adverse Event Management Strategies

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ABSTRACT

Introduction: Vandetanib has recently demonstrated clinically meaningful benefits in patients with unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). Given the potential for long-term vandetanib therapy in this setting, in addition to treatment for disease-related symptoms, effective management of related adverse events (AEs) is vital to ensure patient compliance and

maximize clinical benefit with vandetanib therapy.

Methods: This expert meeting-based review aims to summarize published data on AEs associated with vandetanib therapy and to provide clinicians with specific practical guidance on education, monitoring, and management of toxicities induced in patients treated with vandetanib in advanced and metastatic MTC. The content of this review is based on the expert discussions from a multidisciplinary meeting held in October 2012.

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Results: Characteristics, frequency, and risk data are outlined for a number of dermatological, cardiovascular, gastrointestinal, and general AEs related to vandetanib treatment. Preventive strategies, practical treatment suggestions, and points for clinical consideration are provided.

Conclusions: Good patient and team communication is necessary for the prevention, early detection, and management of AEs of vandetanib. Physicians, nurses, and other healthcare providers play a critical role in providing AE management and patient support to optimize outcomes with vandetanib in MTC.

Keywords: Adverse effects; Antineoplastic agents/adverse effects; Cardiovascular; Dermatology; Medullary thyroid cancer; Medullary thyroid carcinoma; Patient safety; Piperidines/therapeutic use; Protein kinase inhibitors; Thyroid neoplasms/drug therapy; Vandetanib

INTRODUCTION

Medullary thyroid carcinoma (MTC) arises from calcitonin-secreting parafollicular cells of the thyroid and accounts for less than 5% of all thyroid cancers [1]. The 10-year survival rate for patients with MTC is 96% if the disease is treated while the tumor is confined to the thyroid gland [2]. Distant metastases are

observed at presentation in 7–23% of patients [1]. Of these, about 40% will die of the disease within 2 years after the diagnosis of distant metastases, whereas about 40% are still alive after 10 years [2]. Altogether, distant metastases are the leading cause of MTC-related death [1].

Until recently, therapeutic options for rare cases of advanced, unresectable MTC have been limited, but advances in the understanding of the pathogenesis of MTC have led to the development of targeted therapies for this disease. Vandetanib is a once-daily oral tyrosine kinase inhibitor (TKI) that selectively targets the rearranged during transfection (RET) proto-oncogene, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR) [3, 4]. Vandetanib (Caprelsa[®], ZD6474; AstraZeneca, Macclesfield, UK) is the first drug approved for the treatment of adult patients with unresectable, locally advanced, or metastatic disease in the United States and Europe [5, 6]. Long-term treatment with vandetanib has demonstrated a statistically significant longer median progression-free survival versus placebo (30.5 vs 19.3 months; $p = 0.001$) in this setting [7]. This underscores the need to anticipate and effectively manage therapy-related adverse events (AEs) that will, in turn, promote patient compliance and, therefore, maximize clinical benefit.

Based on clinical studies, the most common AEs reported for vandetanib in MTC are diarrhea, rash and folliculitis, nausea, corrected QT interval (QTc) prolongation, hypertension, and fatigue [7–9]. Endocrine effects evidenced by increased thyroxine, calcium, and vitamin D analog requirements have also been noted [10]. The majority of AEs are manageable according to standard clinical practice alone or in combination with vandetanib dose reductions, and data indicate that severe AEs are not sustained over the course of treatment [11].

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In the Phase III Zactima Efficacy in Thyroid Cancer Assessment (ZETA) study, patients with locally advanced or metastatic MTC were randomized 2:1 to vandetanib 300 mg/day ($n = 231$) or placebo ($n = 100$) [7]. Vandetanib treatment led to a significant increase in the primary endpoint of PFS [hazard ratio 0.46, 95% confidence interval (CI) 0.31–0.69, $p < 0.001$, median follow-up 24 months] versus placebo [7]. The median PFS was 19.3 months in the placebo group, compared with a predicted median PFS of 30.5 months for vandetanib [7]. Vandetanib also demonstrated significantly high rates of objective response (45% versus 13% for placebo; $p < 0.001$), disease control (87% versus 71%; $p = 0.001$), and calcitonin biochemical response (69% versus 3%; $p < 0.001$) [7]. Furthermore, vandetanib was also active in patients with sporadic disease and no detectable RET mutations [7], suggesting that the presence of a RET mutation is not a prerequisite for patients to benefit from treatment [11].

Diarrhea, hypertension, prolongation of the QTc, and fatigue were the most commonly reported (incidence $>5\%$) treatment-emergent grade 3+ AEs in the ZETA trial [7]. Additionally, patients required an increase in thyroid hormone replacement (vandetanib, 49.3% vs placebo, 17.2%). Nearly all patients experienced at least one AE and 55% experienced a grade 3 or higher AE [11]. Most AEs occurred 3–6 months after treatment initiation [11]. Despite the frequency of dose reductions [35% (81/231)] needed with vandetanib, only 12% (28/231) of patients discontinued treatment due to AEs [7].

Rash is the most frequently reported dermatologic AE in vandetanib treatment, occurring in more than 45% of vandetanib-treated patients with MTC in the ZETA trial and is second only to diarrhea [7]. Gastrointestinal (GI) AEs included diarrhea (56%), nausea (33%; 11% grade 3+), decreased appetite (21%),

vomiting (14%), and abdominal pain (14%) [7]. Fatigue and asthenia were reported by 24% and 14% of vandetanib-treated patients in ZETA, respectively.

QTc prolongation >500 ms (any grade) was reported by 14% of vandetanib-treated patients in ZETA versus 1% of those receiving placebo [7]. No cases of Torsades de Pointes (TdP) were reported [7], although two patients in a wider drug-safety database had QTc intervals >550 ms (one due to sepsis and one due to heart failure) [6]. In a systematic review and meta-analysis involving patients with a range of tumors ($n = 2,188$), the overall incidence of all-grade and high-grade QTc interval prolongation with vandetanib 300 mg once-daily was 16.4% (95% CI 8.1–30.4%) and 3.7% (95% CI 1.7–7.8%), respectively, among patients with non-thyroid cancer, and 18.0% (95% CI 10.7–28.6%) and 12.0% (95% CI 4.5–28.0%), respectively, among patients with thyroid cancer [12]. Treatment discontinuations due to QTc prolongation (0.9%) and hypertension (0.9%) have been reported [13].

In this review, we aim to summarize data in the literature on AEs associated with vandetanib therapy and provide community healthcare providers with specific practical guidance on patient education, monitoring, and management of patients taking vandetanib for MTC.

DISCUSSION

The Need for Optimal Management of Vandetanib Therapy in MTC

As the majority of patients who respond to vandetanib are likely to receive this TKI for extended periods of time, all care providers, including community healthcare physicians

and nurses, need to have a good understanding of the drug's safety profile and its potential impact on quality of life and compliance with the drug.

Prior to initiating therapy, a review of past medical history, current comorbidities, and medications should be conducted, with an emphasis on the potential interactions and effects on vandetanib-related AEs. There is controversy in the literature regarding the optimal time to start tumor treatment in patients with advanced MTC [1]. The size and number of tumor foci, and the rate of change of tumor volume during watchful waiting, may help identify the optimal time to commence treatment with vandetanib [6]. The rate of change in serum levels of calcitonin and/or carcinoembryonic antigen may also be taken into account but should not be considered in isolation. Table 1 shows a pragmatic consensus of when to start systemic treatment in patients with advanced MTC.

Vandetanib is typically given initially in MTC as a once-daily 300 mg capsule taken with or without food at about the same time

Table 1 Decision matrix for initiating vandetanib treatment in unresectable, locally advanced, or metastatic medullary thyroid cancer

Progression ^a	Tumor burden	
	Small	Large
<12–14 months	Clinical judgment	Yes
>12–14 months	No	Clinical judgment ^b

Based on expert discussions; please refer to local prescribing information and guidelines before prescribing vandetanib

^a Assessed via Response Evaluation Criteria in Solid Tumors (RECIST)

^b Considerations: vandetanib could be started as systemic treatment, if there is a high standardized uptake value on fluorodeoxyglucose positron emission tomography scan; or in the presence of symptoms (e.g. diarrhea, weight loss, pain, dyspnea, tiredness); or if the tumor or metastases located at a particular site are potentially harmful

each day [5, 6], which may contribute to patient acceptance and adherence. The prolonged half-life of vandetanib (19 days) is a factor for consideration in the management of any potential AEs [6]; pharmacokinetic data for the drug are published elsewhere [14]. Local prescribing information should be consulted for full details of dosage and administration guidelines for vandetanib therapy.

Dose reduction may result in rapid AE improvement, suggesting a direct toxic effect of the agent. For grade 3 or 4 AEs, vandetanib is discontinued until AEs resolve, after which vandetanib therapy is resumed at a lower dose. Efficacy is observed at doses lower than 300 mg/day [15], and for long-term treatment finding a dose that is well tolerated and allows a normal quality of life may be the best way to ensure patient compliance and avoid self-made adjustments to medication.

Management of Dermatological AEs

Patients who receive vandetanib are at risk of developing a rash (Fig. 1). In a systematic review of trials involving 2,961 patients with a range of tumors, including MTC, the incidence of all-grade and high-grade rash/folliculitis associated with vandetanib 300 mg was 46% (95% CI 40.6–51.8%) and 3.5% (95% CI 2.5–4.7%), respectively [16]. The mechanism of the rash has not been fully elucidated, but most observed rashes, especially those presenting as follicular pustules (Fig. 2), are probably due to the anti-EGFR action of vandetanib, as anti-EGFR agents are associated with acute and subacute folliculitis [17]. It is thought that the ability of vandetanib to block EGFR triggers follicular hyperkeratosis, leading to follicle obstruction and an inflammatory response [18]. There is also a risk of superinfection of these skin lesions.



Fig. 1 Examples of rash seen with vandetanib treatment in patients with metastatic medullary thyroid cancer. **a** Rash on hands and forearms; **b** photosensitivity rash on upper extremity and back



Fig. 2 Example of folliculitis in a patient treated with vandetanib. **a** Back; **b** front

Other cutaneous AEs observed with vandetanib treatment include photosensitivity, xerosis, finger clefts, paronychia, genital skin

reactions, subungual splinter hemorrhages, and blue-gray macules [17]. Photosensitivity is observed in all patients, even through glass



Fig. 3 Example of blue-gray macules on the forehead of a patient treated with vandetanib. *Arrows* indicate small spots on a greyish background

behind closed windows, and should be prevented by protection against any sun exposure. Blue-gray macules can be of variable size and are usually located on the face, scalp, or trunk (Fig. 3). They are very similar to the pigmented macules observed on the skin and cornea of patients receiving amiodarone [19], which appear after several months of treatment and usually disappear after treatment interruption. Mucositis, erythrodysesthesia, and hand-foot skin reactions are rare and usually minor [17]. Rarely, serious skin reactions such as Stevens–Johnson syndrome and erythema multiforme have been reported [20].

Cosmetically, dermatologic AEs can be debilitating and may adversely affect patients' quality of life [21], potentially resulting in either interruption or discontinuation of treatment. EGFR inhibitor-related skin toxicity has been associated with a dose reduction in 60% of patients and treatment withdrawal in 32% [22]. Dermatologic AEs led to treatment discontinuation much less frequently in vandetanib-treated patients with MTC than with other treatment options, with rash (1.3%), eczema (0.4%), photosensitivity reactions (0.4%), and pruritus (0.4%) [13].

Although frequent, dermatologic AEs are generally manageable. Before starting vandetanib treatment, it is critical to discuss the potential development of skin reactions with patients, initiate preventive measures, and provide reassurance that these can usually be managed effectively. An evaluation of mucosal and skin surfaces is recommended whenever patients attend clinic. Key management points include strict photoprotection (e.g. use of a broad-spectrum UVA/UVB sunscreen with a sun protection factor of 30 or higher, avoidance of any sun exposure by cloth protection) and avoidance of products that dry the skin (e.g. soaps, alcohol-based or perfumed products). Early monitoring is essential to capture the emergence of rash, which is generally treatable. Collaboration with a dermatologist may be needed in severe or complicated cases. Questions to consider when dealing with a rash are listed in Table 2. An extensive review of commonly used topical and systemic therapies to treat skin-related AEs induced by vandetanib is shown in Table 3 [23–26].

Management of Cardiovascular AEs

Increased blood pressure and QTc prolongation have been observed in patients taking vandetanib. Based on a systematic review and meta-analysis of 3,154 patients receiving vandetanib, the incidences of all-grade and high-grade hypertension were 24.2% (95% CI 18.1–30.2%) and 6.4% (95% CI 3.3–9.5%), respectively [27]. Patients with MTC also had a higher incidence of all-grade events than patients with non-small cell lung cancer (NSCLC) and non-MTC/NSCLC tumors receiving vandetanib, with a relative risk of 1.36 (95% CI 1.05–1.76, $p = 0.02$) and 2.06 (95% CI 1.26–3.36, $p = 0.004$), respectively,

Table 2 Topics that should be discussed with and carefully explained to all patients before receiving vandetanib to avoid or reduce the frequency of rash, diarrhea and other potential vandetanib-related adverse events, and the level of disturbance to quality of life, through awareness and early prevention by the patient

Rash

Are there any indicators of severe disease (e.g. systemic symptoms, eosinophilia, mucosal lesions, bullous lesions, epidermal detachment)?

Is the rash related to vandetanib treatment? Consider alternatives (e.g. infection, other concomitant therapies)

Will treatment interruption be required? Prescribe local and/or systemic treatments

Diarrhea

Obtain a clear picture of the clinical course of diarrhea, including onset, duration, number of stools, and stool composition

Perform an abdominal examination

Assess for signs of dehydration (e.g. dry mouth and skin, dizziness, weakness, decreased urine output, low blood pressure, tachycardia)

Obtain medications and dietary profile to identify diarrhea-causing agents and/or diarrhea-enhancing foods

Monitor closely for and correct serum electrolyte imbalances

For uncomplicated diarrhea, provide supportive advice

Stop all lactose-containing products, alcohol and high-osmolar supplements until diarrhea is controlled with uncomplicated medications

Drink 8–10 glasses of water or clear liquids a day (e.g. broth)

Eat small frequent meals (e.g. bananas, rice, apple sauce, toast, plain pasta)

Treatment with loperamide (one pill after each stool) and codeine

For severe diarrhea, vandetanib should be stopped until diarrhea improves and then resumed at a reduced dose [6]

For persistent diarrhea after cessation of vandetanib, a stool workup for blood, infectious causes, and fecal leukocytes should be performed if possible

Considerations for patient education

Provide clear and easily understandable guidance on what to do and who to contact if an adverse event occurs in between visits to the treating clinic

Ask patients to contact the clinic if new side effects develop

Remind patients to contact the clinic if any new medications are prescribed by other healthcare providers

Teach patients how to measure blood pressure or ensure this is monitored regularly (e.g. at a general practice or by the patients themselves)

Explain the necessity for frequent ECG and serum electrolyte monitoring

Ensure patients are aware of potential vandetanib-related adverse events (e.g. diarrhea, rash) and provide relevant advice (e.g. dietary recommendations, skincare guidelines)

ECG electrocardiogram

Table 3 Management of dermatologic adverse events related to vandetanib therapy

Adverse event	Description	Recommended treatment	Comments
Rash [24]	Mild Usually localized Minimal symptoms No impact on ADL No sign of superinfection	No treatment or topical hydrocortisone 1% or 2.5% cream and/or clindamycin 1% gel	Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step
	Moderate Generalized Mild symptoms (e.g. pruritus, tenderness) Minimal impact on ADL	Hydrocortisone 2.5% cream or clindamycin 1% gel + doxycycline 100 mg BID	Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step
	Severe Generalized Severe symptoms Significant impact on ADL Potential for superinfection	Treatment interruption Hydrocortisone 2.5% cream or clindamycin 1% gel + doxycycline 100 mg BID + methylprednisolone dose pack	Reassess after 2 weeks; if reactions worsen, consider dose interruption or discontinuation
Pruritus [23]	Often accompanies rash at onset Can occur as a consequence of dry skin	Treat underlying condition first (e.g. rash, xerosis) Topical menthol 0.5%/pramoxine 1%/doxepin	Follow gentle skin care instructions Topical antihistamines and lidocaine are not recommended as they can become allergens, and can be absorbed systemically
		Medium- to high-potency topical steroids (triamcinolone acetone 0.025%, desonide 0.05%, fluticasone propionate 0.05%, alclometasone 0.05%) Systemic antihistamines Systemic gabapentin/pregabalin Systemic doxepin	Use non-sedating systemic antihistamines first; adjust for renal impairment as needed Gabapentin/pregabalin are recommended as second-line treatment only if antihistamines fail

Table 3 continued

Adverse event	Description	Recommended treatment	Comments
Xerosis [23]	Dry skin, often accompanying or succeeding rash	Emollient fragrance- and irritant-free creams	Prevent using bathing techniques (e.g. bath oils, mild moisturizing soaps, tepid water) and regular moisturizing creams
	Usually occurs 30–60 days into treatment	Occlusive emollients containing urea, colloidal oatmeal, or petroleum-based creams	Avoid extreme temperatures and direct sunlight
	May develop into xerotic dermatitis and predispose to skin fissures	Urea creams	Avoid alcohol-containing lotions, retinoids, or benzoyl peroxide
		Salicylic acid 6%	Use caution when using greasy creams on the face and chest
		Zinc oxide (13–49%)	Apply exfoliants to intact skin only as exfoliants may sting or burn when applied to eroded or erythematous skin
		Exfoliants for scaly areas (e.g. ammonium lactate 12%, lactic acid cream 12%)	
Paronychia [23]	Tender, edematous, often purulent inflammation of the nail folds	Ultrapotent topical corticosteroids	Prevent with diluted bleach soaks (approximately 0.005%)
	Fingernails and toenails may be affected, with the first digits most commonly affected	Topical silver nitrate	Avoid of irritants and trauma (e.g. use comfortable shoes)
		Biotin for brittle nails	Avoid use of empiric antibiotics without culture of skin lesions
		Antimicrobials for culture-proven infection	Antifungals are not recommended
		Weekly chemical cauterization with silver nitrate, electrodesiccation, or nail avulsion to eliminate excessive granulation tissue	Reserve antimicrobials for culture-proven infection

Several classifications of chemotherapy-related dermatologic effects are currently available, including the Multinational Association of Supportive Care in Cancer EGFR1 Skin Toxicity Tool [25] and the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE) [26] scale *ADL* activities of daily living, *BID* twice daily

probably due to longer treatment exposure at higher doses [27].

Early detection and effective management of hypertension according to current guidelines is recommended, with close monitoring of blood pressure during the first months of treatment. Pre-existing hypertension should be managed carefully before treatment initiation in line with current guidelines, such as those from the fifth joint task force of the European Society of Cardiology, who define hypertension as blood pressure $\geq 140/90$ mmHg [28]. Angiotensin-converting-enzyme (ACE) inhibitors are the

most commonly recommended anti-hypertensive drugs for patients under vandetanib treatment. Calcium antagonists and beta-blockers are also helpful if hypertension is not controlled with ACE inhibitors alone. Blood pressure monitoring 1–3 times per month may be done by the patients themselves to allow for close control of hypertension without the need for specific hospital visits.

The AE of most concern with vandetanib is QTc prolongation, particularly in view of the long terminal elimination half-life of the drug

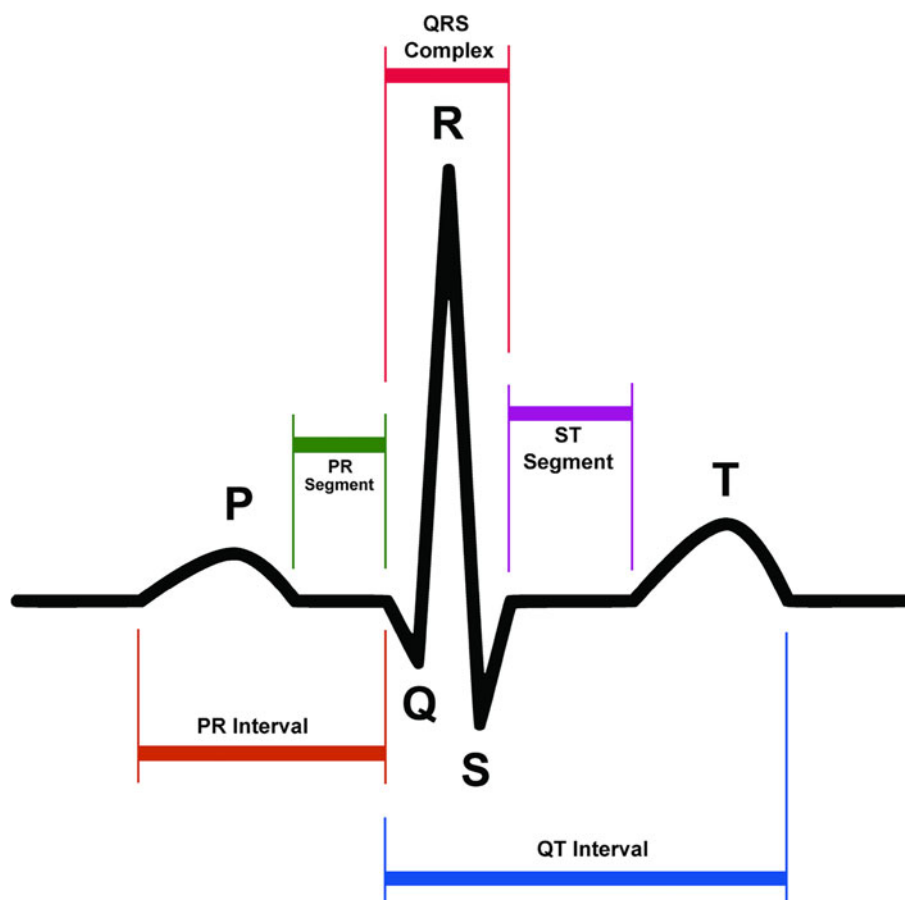


Fig. 4 Schematic representation of normal electrocardiographic trace. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on an ECG trace. Generally speaking, it represents electrical depolarization and repolarization of the left and right ventricles. A prolonged QT interval is a biomarker for

ventricular tachyarrhythmias such as Torsades de Pointes and is a risk factor for sudden death. As the QT interval is influenced by heart rate, the relative risk interval preceding the QT interval is measured to correct for this. *ECG* electrocardiogram

[6]. The term “corrected” QT interval may be misunderstood. It relates to the QT interval but is adjusted for heart rate (Fig. 4). Definitions for QTc interval prolongation vary in the literature, and prolongation is characterized either in absolute (e.g. >500 ms) or relative terms (e.g. >30 ms change from baseline in QTc interval). In general, an interval of above 480 ms is considered prolonged.

Accurate measurement of the QTc interval is best performed manually, rather than relying on automatic measurements of standard ECG machines, to guide treatment with QTc-prolonging drugs [29]. Correction formulae such as Bazett’s square root formula ($QTc = QT/RR^{1/2}$) are frequently used but are often inaccurate at the extremes of physiological heart rate [29]. Use of a QT nomogram, which consists of a plot of QT versus heart rate, is an alternative approach. A QT interval–heart rate pair that plots above an “at-risk” line indicates that the patient is at risk of TdP (Fig. 5) [30].

QTc prolongation above 450 ms is associated with a risk of ventricular arrhythmias (e.g. TdP, syncope, and sudden death), and the risk rises with increasing durations of prolongation. First QT prolongations occur most often in the first 3 months of treatment with vandetanib [6].

It is recommended that vandetanib should be withheld if the QTc interval is longer than 500 ms until it returns to 450 ms, upon which a reduced dose can be resumed [5]. A baseline ECG with QTc measurement must be recorded prior to initiation of vandetanib, and vandetanib should not be given to patients with a baseline QTc >450 ms (value may vary depending on local product information). During vandetanib treatment, mean prolongation of QTc is 30 ms. Monitoring of the QTc should be performed at least once every month for the first 3 months on the drug. Vandetanib therapy should be withheld and the patient referred to a cardiologist as soon as any new abnormality following the start of vandetanib treatment is detected. Depending

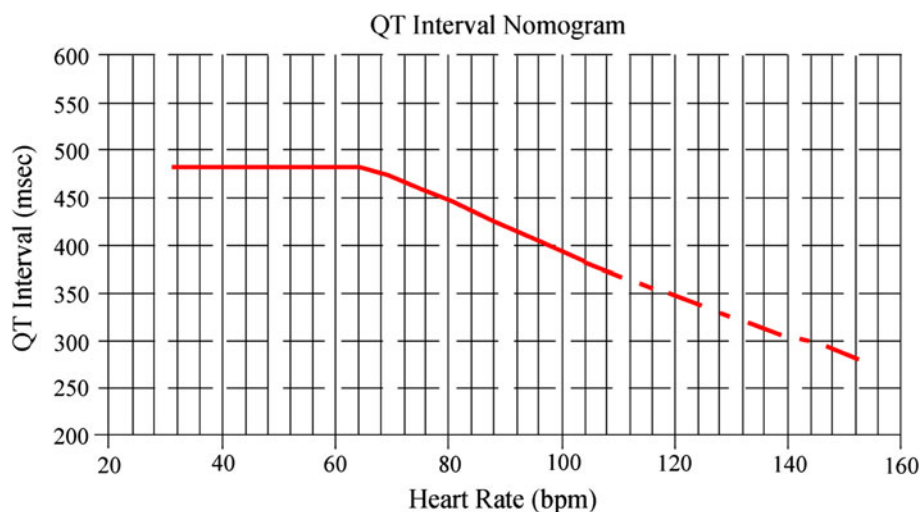


Fig. 5 QTc interval nomogram for determining ‘at risk’ QTc–heart rate pairs from a single 12-lead ECG [30]. Reproduced with permission of The Association of Physicians from Chan et al. [30]. © Oxford University Press. Use: the QTc interval should be measured manually on a 12-lead ECG from the beginning of the Q wave until the

end of the T wave in multiple leads (i.e. six leads including limb and chest leads and median QT calculated). The QTc interval is plotted on the nomogram against the heart rate recorded on the ECG. If the point is above the line then the QTc–heart rate is regarded as “at risk”. ECG electrocardiogram, QTc corrected QT

on the clinical situation, close attention to the QTc and even Holter monitoring may be required. Table 4 outlines the principles of managing hypertension and QTc interval prolongation.

The mechanisms of specific cardiovascular AEs in patients with MTC may differ from other tumor types and can limit therapeutic options for other AEs or comorbidities. Factors that may be associated with QTc prolongation include baseline QTc interval, electrolyte levels, and the use of concomitant drugs. It should also be

remembered that thyroid function disorders can lead to QTc prolongation and, therefore, need correction [31]. Diarrhea may affect electrolyte balance, necessitating close monitoring of serum potassium, magnesium, and calcium, and this may play a role in the higher incidence of high-grade QTc interval prolongation with vandetanib in thyroid versus other tumor types. Table 5 lists agents that are contraindicated or not recommended for coadministration with vandetanib; an updated list of agents that prolong QTc and/or induce

Table 4 Management of cardiovascular adverse events related to vandetanib therapy

Adverse event	Recommendations	Notes
Hypertension [6, 11]		
Before treatment	Blood pressure should be recorded at baseline Blood pressure should be stabilized according to standard medical practice	In clinical trials, treatment with vandetanib did not worsen hypertension in patients who had required antihypertension treatment at baseline
During treatment	Blood pressure should be monitored and controlled as appropriate If high blood pressure cannot be controlled with medical management, vandetanib should not be restarted until blood pressure is medically controlled Reduction of vandetanib dose may be necessary	Treatment may be resumed once hypertension is appropriately controlled
QTc prolongation [6, 11]		
Before treatment	An echocardiogram, ECG, and levels of serum potassium, calcium, and magnesium and TSH should be obtained at baseline	Vandetanib treatment must not be started in patients with QTc >450 ms (US prescribing information [5]; >480 ms in EU summary of product characteristics) [6]
	Hypocalcemia, hypokalemia, and/or hypomagnesemia must be corrected prior to vandetanib administration	Vandetanib should not be given to patients with congenital long QTc syndrome or a history of TdP unless all risk factors that contributed to TdP have been corrected Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction An annual echocardiogram may be useful for patients at high cardiovascular risk (e.g. elderly with diabetes)

Table 4 continued

Adverse event	Recommendations	Notes
During treatment	An ECG, and levels of serum potassium, calcium, and magnesium and TSH should be obtained at 1, 3, 6, and 12 weeks after starting treatment and every 3 months for at least a year thereafter	Serum TSH, serum potassium, serum magnesium, and serum calcium should be kept within normal range
	This schedule should apply to the period after dose reduction due to QTc prolongation and after dose interruption for more than 2 weeks	Coadministration of substances known to prolong QTc is contraindicated or not recommended; in particular, the concomitant use of vandetanib with ondansetron is not recommended
	ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards, with frequent monitoring of the QTc interval	If antiemetic therapy is required, consider palonosetron-based treatment
	Additional monitoring of QTc, electrolytes, and renal function is needed in case of diarrhea, increase in diarrhea/dehydration, electrolyte imbalance, and/or impaired renal function	If QTc increases markedly but stays below 500 ms, cardiologist advice should be sought
	Discontinue vandetanib in patients who develop a single value of a QTc interval ≥ 500 ms	
	Dosing can be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed and any possible electrolyte imbalance has been corrected	

ECG electrocardiogram, QTc corrected QT interval, TdP Torsades de Pointes, TSH thyroid stimulating hormone

TdP may be found at the Arizona Center for Education and Research on Therapeutics (AZERT) CredibleMeds® website [32]. QTc prolongation is rarely a problem when preventive measures are applied, including avoidance of drugs known to prolong the QTc interval, and when hypothyroidism, hypokalemia, hypomagnesemia, and hypocalcemia are corrected.

Management of Gastrointestinal AEs

Table 6 outlines the recommended treatment and other management considerations for

gastrointestinal AEs, which include nausea, vomiting, and diarrhea.

Substances used to manage chemotherapy-induced nausea and vomiting include 5-HT3 receptor antagonists (also known as setrons), dopamine D2 antagonists, and steroids (dexamethasone 8 mg twice daily).

In general, 5-HT3 antagonists are associated with the potential to increase the QTc interval. The use of ondansetron should be avoided in patients being treated with vandetanib, particularly those who have cardiovascular disease and a high risk of drug-induced TdP as well. When used in patients with cardiovascular

Table 5 Selection of agents that are contraindicated or not recommended for coadministration with vandetanib

Contraindicated	Not recommended
Arsenic	Amisulpride
Cisapride	Chlorpromazine
Class IA and III antiarrhythmics	Halofantrine
Intravenous erythromycin	Haloperidol
Mizolastine	Lumefantrine
Moxifloxacin	Methadone
Toremifene	Metoclopramide
	Ondansetron
	Pentamidine
	Sulpiride
	Zuclopenthixol

As recommended in the vandetanib summary of characteristics [6]

disease with one or more risk factors for TdP, ondansetron increased the QTc interval by about 19 ms for up to 120 min after administration [33]. Palonosetron represents a new generation of setrons and possesses the highest affinity for the 5-HT₃ receptor in this class with the longest half-life of ~40 h [34, 35]. In two small studies of patients receiving chemotherapy, palonosetron did not cause severe rhythmic disorders or symptomatic electrocardiogram (ECG) changes [36], or a statistically significant increase in median QT minimum value [37]. Palonosetron may, therefore, be considered an alternative antiemetic therapy. Nevertheless, caution should be exercised in its concomitant use with medicinal products that increase the QTc interval or in patients who have or are likely to develop prolongation of the QT interval. As palonosetron may increase large bowel transit time, patients with chemotherapy-induced diarrhea could benefit from this substance [34].

The antiemetic action of metoclopramide is based on its D₂ receptor antagonist activity. However, at higher doses the substance also exerts 5-HT₃ antagonist activity. Thus, metoclopramide may be associated with QTc prolongation and should be used with caution only [38].

Aprepitant is a neurokinin 1 (NK1) receptor antagonist that is available for chemotherapy-induced nausea and vomiting [39]. Signals indicating QT-prolonging properties could not be derived so far from 15 pharmacologic studies [40].

Diarrhea, either due to the disease or treatment, can impair quality of life in patients with MTC, resulting in dose reduction, interruption, or discontinuation of therapy. It may also put patients at risk of dehydration with electrolyte disturbance and other potentially life-threatening complications due to the QTc prolongation associated with vandetanib. Diarrhea frequently worsens during antibiotic therapy that may be given for folliculitis.

Diarrhea may also exist in MTC because of the production of hormones that accelerate gastrointestinal motility and may improve with vandetanib treatment. In addition, the use of agents that slow peristaltic movements (e.g. loperamide) or mild opioids (e.g. codeine) can provide relief that is usually partial. Evidence on the efficacy of somatostatin analogs against diarrhea in patients with MTC is not available.

As with other types of AEs, awareness and education regarding GI tolerability is a key part of patient education. Typical measures to take when confronted with diarrhea are listed in Table 2. QTc prolongation can also occur with hypokalemia; therefore, regular monitoring of serum electrolytes is essential. In case of severe GI symptoms, vandetanib should be stopped

Table 6 Management of gastrointestinal adverse events related to vandetanib therapy

Adverse event	Description	Recommended treatment	Comments
Nausea and vomiting	Mild Loss of appetite without alteration in eating habits	Patient should eat foods that are soft and easy to digest rather than heavy meals	Patient should avoid eating in a room with cooking odors or that is very warm
	1–2 episodes (separated by 5 min) in 24 h	Patient should eat several small meals per day rather than only one or two large meals per day	
		Metoclopramide 10 mg every 8 h may be administered	
	Moderate Oral intake decreased without significant weight loss, dehydration or malnutrition	Metoclopramide 10 mg every 8 h may be administered	
	3–5 episodes (separated by 5 min) in 24 h	5-HT3 receptor antagonists (also known as setrons), dopamine D2 antagonists, and steroids (dexamethasone 8 mg twice daily) are not commonly needed	
	Severe Inadequate oral caloric or fluid intake	Hospitalization is needed	Tube feeding or parenteral nutrition may be needed
	6 or more episodes (separated by 5 min) in 24 h	Control renal function and hydroelectrolytes Replace fluids and electrolytes	
		Neurokinin 1 receptor antagonist such as aprepitant can be used	

Table 6 continued

Adverse event	Description	Recommended treatment	Comments
Diarrhea	Mild Increase of less than 4 stools per day over baseline	Ensure correct hydration Educate patient about a stringent diet Loperamide 2 mg to be taken after every fecal deposit up to a maximum of 16 mg per day	Patient should have loperamide with them at all times since diarrhea may appear at any time Advise patient to avoid overeating and in particular high-fibre or spicy food Advise patient to eat broths, soups, bananas, and canned fruits to help replace salt and potassium lost by diarrhea Advise patient to avoid greasy foods, very hot or cold liquids, caffeine, milk and milk products, food and drinks that cause gas (e.g. peas, lentils, cruciferous vegetables, chewing gum, soda), and sugar-free candies or gum made with sorbitol
	Moderate Increase of 4–6 stools per day over baseline	Ensure correct hydration Loperamide 2 mg to be taken after every fecal deposit up to a maximum of 16 mg per day	Moderate diarrhea can impact on a patient's daily social life Dedicate time to avoid patient depression and anxiety Patient should drink at least a cup of liquid after each loose bowel movement
	Severe Increase of 7 or more stools per day over baseline	Hospitalization is needed Control renal function and hydroelectrolytes Replace fluids and electrolytes	

until symptoms improve. In severe diarrhea persisting after cessations of treatments, a stool work-up should be performed to exclude organic causes.

Management of Generalized AEs

The effect of generalized AEs on quality of life can vary. While many patients are able to maintain normal activity schedules, others experience debilitating fatigue that leads to dose limitation or treatment discontinuation [13]. Fatigue comprises emotional, physical, and/or cognitive tiredness and can be a distressing and persistent AE. It is usually multifactorial and may arise as a symptom of the underlying burden of disease, hypothyroidism, anemia, depression, sleep disturbances, or pain, and can thus be difficult to address. Management of fatigue is primarily supportive; however, it is important to identify treatable causes contributing to it. Patients should be assessed for depression and appropriate treatment measures (avoiding drugs that may prolong QTc) should be introduced to optimize emotional and social support.

Vandetanib treatment in patients with MTC increases visceral fat and muscle body content, in contrast to other TKIs [41]. This positive effect should be taken into consideration and patients on vandetanib should be encouraged to follow a normal social and professional life, and participate in sports activities. It is worth noting that pregnancy constitutes a contraindication for vandetanib therapy and effective contraception is necessary for all patients.

Other AEs reported with vandetanib therapy include reversible posterior leukoencephalopathy syndrome, which requires treatment withdrawal, and cornea verticillata, which is responsible for blue vision and regresses with dose reduction [5].

Nursing Care for Patients Receiving Vandetanib for MTC

As an integral part of a multidisciplinary care team, an experienced specialist nurse is in a unique position to facilitate early detection, intervention, and coordinated management of AEs arising with vandetanib treatment. As a number of AEs are typically seen in the first 3 months of vandetanib treatment, close patient contact is important during this period. Clinic visits may be scheduled every 2 weeks for the first 6–8 weeks to accommodate ECG, serum electrolyte monitoring, and review of emerging AEs.

Apart from providing vital patient education (Table 2), specialist nurses are typically faced with the challenges of eliciting AE information from patients. While some patients may feel more comfortable discussing AEs with a nurse rather than a physician, not all patients realize the importance of reporting specific symptoms and they may not contact the clinic if they experience AEs during treatment. Therefore, it is important that patients are made aware, often by the specialist nurse, of symptoms to look out for and the value of reporting at an early stage. A list of drugs that should be avoided during vandetanib treatment should be given to the patient so that any care provider can check whether a drug can be safely given or not and, in case of doubt, contact a specialist nurse or physician. In addition, patients must be made aware of the importance of informing their specialist nurse and/or physician of any concomitant medication started by other clinicians for comorbidities. These should be carefully documented and cross-checked to avoid possible dangerous drug interactions.

Oncology nurses also have to deal with the logistical impact of geographical distance on patient visits. With the rarity of MTC, it is not

Table 7 Pocket guidelines for the management of adverse events with vandetanib

Adverse event	Patient education before starting treatment	At the time adverse event emerges
Skin toxicity	Prophylactic use of hydrating creams all over the body, especially areas of sun-exposed skin and hands and feet	Early use of fatty ointments and urea creams. If no improvement, the addition of topical steroids, with or without antibiotics, could be helpful. The oral administration of cloxacillin and anti-histamines also may help
Diarrhea	Patient education with dietary measures	As soon as diarrhea is apparent, oral hydration and anti-diarrhea medications such as loperamide 2 mg, taken after every fecal deposit up to a maximum of 16 mg per day, is required. Special care should be taken with elderly patients who have a higher risk of dehydration
Nausea and vomiting	Patient education with dietary measures	Common antiemetics such as metoclopramide or ondansetron are not recommended to prevent or relieve vomiting and nausea. There is a need to ensure correct hydration
Fatigue and asthenia	Treat underlying factors according to standard medical practice that may induce or promote fatigue Advise patients to maintain a healthy diet and to take moderate exercise	Monitor for possible comorbidities that could contribute to fatigue
Mucositis and/or stomatitis	Recommend patients to switch to a mild toothpaste and a soft toothbrush	Rinse mouth with water and use alcohol-free mouthwash Use lip creams or balms Avoid alcohol, acidic food and drink, and excessively hot (temperature) food
Hypertension	Blood pressure should be checked and controlled appropriately Educate patients to measure blood pressure and to recognize the most common symptoms of hypertension	Prescribe anti-hypertensive medication such as ACE inhibitors

ACE angiotensin-converting-enzyme

unusual for patients to live far away from tertiary care specialist clinics. This may necessitate contact via telephone as a replacement for a clinic visit. If required, a visit from an experienced oncology nurse can be substituted for a doctor's appointment.

Alternative options to ensure open patient communication (e.g. a telephone dedicated by the clinic as a helpline, internet video calls, call center) may be considered, subject to the clinic's policies and resources. Through effective use of clinical knowledge, patient

assessment, and advocacy skills, nurses play a key role in the care of patients with MTC.

SUMMARY AND CONCLUSION

Vandetanib has recently demonstrated clinical benefit in patients with MTC [7]. Other promising agents are in clinical development, and sequencing strategies are likely to expand treatment options and translate to improved survival outcomes in the near future. Patients will potentially receive vandetanib in addition to supportive treatment for comorbidities over a period of several months or years, presenting a unique situation compared with the management of other solid tumor types. With the prospect of longer life expectancy, quality of life is likely to be a determining factor for treatment compliance.

This review proposes pragmatic guidelines for management of AEs related to vandetanib therapy for MTC. For those community physicians who may only treat one or two of these patients per year, we suggest following the “Pocket guidelines for management of vandetanib adverse events” reflected in Table 7.

As with many other targeted cancer therapies, vandetanib is associated with a number of AEs; however, these are generally mild and readily manageable. Informed consent and education about potential treatment-related AEs will help patients anticipate and recognize any tolerability issues with the drug, and active monitoring will allow for early detection and control of AEs that arise. A multidisciplinary approach is strongly recommended, with close coordination and care of patients and their individual needs. These patients have complex requirements and should be treated holistically. The multidisciplinary team, therefore, plays a

critical role in providing optimal AE management and patient support to optimize treatment outcomes in this setting.

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