Safety and efficacy of vandetanib in the treatment of medullary thyroid cancer

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Abstract
Medullary thyroid cancer (MTC) is a rare malignancy affecting the calcitonin producing cells of the thyroid gland. Surgery is the mainstay of treatment in early stages. However in advanced or metastatic disease, there are few efficacious therapies. Recently emerging targeted treatments have shown promising results in this disease. Two such therapies, vandetanib and cabozantinib, have recently been FDA approved for the treatment of locally advanced or metastatic medullary thyroid cancer. Vandetanib is an inhibitor of the RET tyrosine kinase, vascular endothelial growth factor receptors and epidermal growth factor receptors. In phase III trials vandetanib was found to prolong progression free survival but was associated with significant morbidity, including sudden death, prolonged QTc interval, skin toxicity, diarrhea, and hypertension. In this review we discuss the safety and efficacy of vandetanib and optimal management of side effects. With continued monitoring of this emerging treatment, medical practitioners will be able to gain a better understanding of the overall efficacy and dose related toxicities of vandetanib in patients with advanced MTC.

Keywords: vandetanib; medullary thyroid cancer; safety; efficacy.

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Introduction
It is estimated that 60,220 men and women will be diagnosed with thyroid cancer this year [1]. Medullary thyroid cancer (MTC) is a rare malignancy encompassing only 1.7% of thyroid cancers [1]. First described in 1959, MTC is associated with the calcitonin producing parafollicular C cells of the thyroid [2–4]. The majority of MTC’s occur sporadically in the 5th and 6th decade of life while 10–20% are closely associated with the hereditary multiple endocrine neoplasia (MEN) type syndromes. Patients often present with a neck mass and if invasion into local structures has occurred they may also present with hoarseness, respiratory distress, or dysphagia. High levels of calcitonin can cause significant diarrhea, flushing, and weight loss [5]. First line treatment for MTC is total thyroidectomy with nodal dissection. Post-surgical ten year survival rates are 70–80% for all types of MTC. Adjuvant external beam radiation has been studied with one study demonstrating recurrence rates of 14% versus 48% in the surgery group alone but significant scarring and local fibrosis may occur [6]. Local recurrences can often be treated with surgery. Unresectable cases may be treated with external beam radiation but few other effective therapies exist for locally advanced or metastatic disease. Standard cytotoxic chemotherapy has generally been ineffective with rare complete responses. Additionally, the significant toxicities associated with cytotoxic chemotherapy (i.e. fatigue, cytopenias, nausea, vomiting, hair loss, organ dysfunction) makes the use of these agents less attractive. The most commonly used single agents include 5-fluorouracil, capecitabine, dacarbazine, and doxorubicin with response rates ranging from 24–29% [7]. Ten year survival rates in patients with metastatic disease is approximately 40%. Given the limited and ineffective treatment options alternative strategies are being investigated.

Activating germline RET mutations are found in more than 95% of hereditary cancers [8]. Activation of RET results in signaling through multiple pathways including RAS, ERK, and SRC [9]. There is a genotypic/phenotypic correlation between the clinical features of these hereditary syndromes (MEN2A, MEN2B, familial MTC) and the type of RET mutation [10]. Other clinical features associated with these syndromes include developmental abnormalities, intestinal gan-

glioneuromas, mucosal neuromas, hyperparathyroidism, and pheochromocytoma. Specific mutations result in specific clinical syndromes including MTC and pheochromocytoma in RET codon 634 mutations or MTC only in RET codon 883 mutations [9].

Another key factor resulting in malignant cell potentiation is vascular endothelial growth factor (VEGF). VEGF plays a key role in angiogenesis resulting in proliferation of blood vessels [11]. It has been found to be overexpressed in patients with thyroid carcinomas, as well as multiple other solid tumors [12, 13]. Epidermal growth factor receptor (EGFR) overexpression has also been noted in patients with MTC [13]. Given the VEGF, RET kinase and possible EGFR involvement in MTC, ZD6474, later to be named vandetanib was developed for treatment of MTC. Vandetanib is a rationally designed oral targeted agent that inhibits RET, VEGFR2, and EGFR. Unlike previous treatment strategies in this disease, this agent specifically targets the molecular pathways that drive the progression of this disease. Based on a phase III randomized controlled trial it was recently approved in April 2011 by the Food and Drug Administration (FDA) for use in metastatic and advanced MTC. In this review we discuss the efficacy and safety of vandetanib.

Vandetanib Mechanism of Action/preclinical Models
The RET proto-oncogene is a transmembrane receptor with an intracellular tyrosine kinase domain. Activation of this results in downstream signaling of several pathways including RAS, RAF, PI3K, ERK, JNK, and NFkB. The end result of this activation in MTC is an inhibition of apoptosis as well as increased cell growth and proliferation [14]. Vandetanib is an orally available agent that was found to inhibit transforming and signaling of RET oncoproteins in vivo [15]. Vandetanib was also found in studies involving human xenografts to block VEGF signaling and in turn neovascularization [16]. Preclinical models have shown inhibition of VEGFR2 as well as EGFR in tumor xenografts. Repression of EGFR signaling was further seen in a non-small cell lung cancer model [17]. These findings illustrate that RET, EGF and VEGF signaling could be inhibited by this targeted agent.

http://www.intermedcentral.hk/
### Efficacy of Vandetanib for Medullary Thyroid Cancer

**Phase I Trials**

There were three phase I trials involving vandetanib. Tamura, *et al.* (2006), conducted a study involving 18 patients with solid tumor malignancies. Varying dosages of vandetanib (100–400 mg) were given daily. Dosing at 200 to 300 mg daily showed objective tumor response in 4 out of 9 patients with non-small cell lung cancer [18]. Holden, *et al.* (2005), performed a dose escalation phase I trial in 75 patients with advanced solid malignancies. Dosing varied widely from 50 to 600 mg daily. Surprisingly no objective responses were seen with any dosage interval [19]. Stable disease was seen in 31 patients (41%) [19]. In a third phase I study, Zhang, *et al.* (2011) gave vandetanib at dosages of 100 mg every other day, 100 mg daily and 300 mg daily, in 36 patients with advanced solid tumors. One patient was noted to have a partial response, interestingly this

### Table 1. Common adverse effects noted in vandetanib trials.

<table>
<thead>
<tr>
<th>Phase of trial</th>
<th>No. of patients</th>
<th>Common side effects</th>
<th>No. of patients with side effects</th>
<th>Trial authors</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>75</td>
<td>Diarrhea</td>
<td>29</td>
<td>Holder, <em>et al.</em> 2005</td>
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<td></td>
<td></td>
<td>Rash</td>
<td>26</td>
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<td></td>
<td>Nausea</td>
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<td></td>
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<td>Hypertension</td>
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<td>Fatigue</td>
<td>14</td>
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<td></td>
<td></td>
<td>Acneiform/maculopapular rash</td>
<td>9/8</td>
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<tr>
<td>I</td>
<td>18</td>
<td>Hypertension</td>
<td>3</td>
<td>Tamura, <em>et al.</em> 2006</td>
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<td></td>
<td></td>
<td>Diarrhea</td>
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<td></td>
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<td>Skin eruption</td>
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<td>Headache</td>
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<td>Elevate alanine transferase</td>
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<td>I</td>
<td>36</td>
<td>Rash</td>
<td>18</td>
<td>Zhang, <em>et al.</em> 2011</td>
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<td></td>
<td>Diarrhea</td>
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<td>Cough</td>
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<tr>
<td>II</td>
<td>19</td>
<td>Diarrhea</td>
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<td>Robinson, <em>et al.</em> 2010</td>
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<td>Fatigue</td>
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<td>Rash</td>
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<td>Constipation</td>
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<td>II</td>
<td>30</td>
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<td>23</td>
<td>Wells, <em>et al.</em> 2010</td>
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<td>III</td>
<td>331</td>
<td>Diarrhea</td>
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<td>Wells, <em>et al.</em> 2012</td>
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<td>Rash</td>
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<td>Hypertension</td>
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<td></td>
<td>Headache</td>
<td>59</td>
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A patient had MTC [20]. Ten patients had stable disease. Overall, all dosages appeared to be tolerated well [20]. These three trials did not show high objective response rates overall. As noted, the only patient to have response in the phase I trial conducted by Zhang, et al. had MTC.

**Phase II trials**

There are two phase II trials that used vandetanib in patients with locally advanced or metastatic MTC. Wells, et al. (2010), conducted a study involving 30 individuals diagnosed with advanced MTC who received 300 mg of vandetanib daily, with 20 of the patients having MEN2A. Twenty percent showed a partial response with 53% showing stable disease greater or equal to 24 weeks from start of treatment. Also of note, calcitonin and CEA levels decreased in greater than 50% of patients (26 and 16 individuals respectively) [21]. Another phase II study conducted by Robinson, et al. (2010), examined the effect of 100 mg oral daily vandetanib in 19 patients with locally advanced or metastatic hereditary MTC who were status post thyroidectomy. Stable disease for at least 24 weeks was seen in 53% of patients with objective response rate of 16% [22]. Biochemical partial response was seen in 16% in regards to decreased serum calcitonin, only 5% (1 patient) was found to have decreased CEA [22]. This showed an inferior response compared to 300 mg vandetanib dosing. Though the lower dose (100 mg daily) of vandetanib showed similar findings in regards to disease stability, biochemical and CEA responses were significantly lower than in patients receiving 300 mg daily.

**Phase III trial**

Wells, et al. (2012) conducted a phase III randomized, double blind trial involving 331 patients with locally advanced or metastatic MTC. Overall 231 patients received vandetanib and 100 patients were placed in the placebo group. This study showed significance in regards to PFS ($P < 0.01$, HR 0.46) with median PFS of 19.3 months in placebo group vs. a possible PFS of 30.5 months in the treatment group (The PFS had not been reached for patients on vandetanib when study was published, with plans to provide a further analysis when 50% of patients had succumbed to illness) [23]. Disease control ($P = 0.01$) and biochemical response ($P < 0.001$) rates also showed significance in those undergoing treatment with vandetanib. These results showed that vandetanib can provide PFS and biochemical response in advanced MTC.

**Safety of Vandetanib**

**Phase I**

The three phase I trials of vandetanib illustrated similar adverse effect profiles. Tamura, et al. who gave 18 patients varying dosages of vandetanib from 100-400 mg, reported dose limiting toxicities including most commonly hypertension (17%), as well as skin eruption, diarrhea, headache which were each seen (6%) of the time (Table 1). They found that dosages of 400 mg or greater of vandetanib exceeded the maximum tolerated dose [18]. Holden, et al. gave 75 patients with advanced solid malignancies vandetanib ranging from 50-600 mg orally daily. Most common side effects seen in patients were diarrhea (29%) and rash (35%). Also seen were nausea, hypertension, fatigue and rash (Table 1). Three out eight patients receiving 500 mg of vandetanib daily developed drug related toxicity [19]. Also of note seven patients receiving 100-600 mg daily developed QTc prolongation. The study reported that 300 mg or less per day of vandetanib appeared to be tolerated best [19]. In the third phase I study discussed here, Zhang, et al. found rash and diarrhea as the most common side effects by far [20] (Table 1). Toxicities including diarrhea, hypertension and rash appear most notably in these three studies. Dosages above 400 mg appear to have the most toxicities and are the least tolerated.

**Phase II**

Vandetanib again showed a variety of side effects in the two phase II trials of locally advanced and metastatic MTC. In a trial involving 300 mg of vandetanib daily performed by Wells, et al. 21 patients required dose reduction with median time to 1st dose reduction being 4.9 months. Grade 3 adverse effects included 6 patients (20%) with prolonged QTc, and 3 patients (10%) each with nausea, diarrhea or hypertension. Commonly seen in greater than 50% of patients were one or more grade 1−2 side effects including: diarrhea, fatigue, nausea or...
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rash (Table 1) [21]. In the second phase II study, Robinson, et al. reported patients having grade 1–2 side effects including diarrhea (47%), fatigue (42%), rash (26%) and constipation (20%) noted in patients receiving 100 mg of vandetanib daily (Table 1). All 19 patients had previously undergone thyroidectomy. Of the 17 patients with baseline TSH levels, all were noted to have increased TSH during treatment, with 2 patients requiring increased thyroid replacement [22]. Six out of the 19 patients (32%) had grade 3 adverse effects with an episode each (5.3%) of: hypertension, asymptomatic QTc prolongation, muscular weakness, pheochromocytoma, diplopia, visual disturbance and myalgia. Vandetanib overall was well tolerated at 100 mg daily dosing with only 2 patients having discontinuation of treatment [22]. The frequency of adverse effects was noted to be increased in the phase II study participants receiving 300 mg daily versus 100 mg daily, with increased grade 3 adverse effects, primarily prolonged QTc. Common other side effects showed similarities to previous studies, such as diarrhea and rash for example.

**Phase III**

The phase III study by Wells, et al. had a median duration of treatment was 90.1 weeks with vandetanib. Most commonly diarrhea (56%), rash (45%), nausea (33%), hypertension (32%) were seen (Table 1). Approximately 20% of patients experienced symptoms such as fatigue, acne, decreased appetite or headache. Thyroid-stimulating hormone serum levels rose, requiring increased thyroid replacement in 49.3 % of patients on vandetanib versus 17.2% in placebo group. Of note, dose reduction was required in 35% versus 3% of patients on vandetanib versus the placebo due to QTc prolongation or other side effects. Documented QTc prolongation on EKG was seen in 14% of patients [23]. Grade 3 or greater adverse effects most commonly presented with diarrhea (25 patients, 11%), HTN (20 patients, 9%) or QTc prolongation (18 patients, 8%) on EKG. Overall rate of discontinuation due to toxicity was 12% over the median treatment duration of 90.1 weeks [23]. Five patients who received vandetanib developed side effects leading to one of each: arrhythmia, acute cardiac failure, respiratory failure, respiratory arrest, aspiration pneumonia and staphylococcus sepsis [23].

**Contraindications:**
- Congenital long QT syndrome

**Warnings:**
* Do not give in patients with torsades de points,
* Uncompensated heart failure or bradyarrhythmias
* Uncompensated heart failure, ischemic cerebrovascular events, Stevens-Johnson syndrome, interstitial lung disease, hemorrhage, reversible posterior leukoencephalopathy syndrome may occur, medication should be immediately discontinued.
* If hypertension or diarrhea occur dose interruption or reduction may be needed
* Renal failure-reduce starting dose to 200 mg in patients with a creatinine clearance < 50 mL/min

**Monitoring**
- Check EKG, serum magnesium, potassium, calcium and TSH at baseline, at 2–4 weeks, 8–12 weeks and then every 3 months *in patients with diarrhea patient should have more frequent testing
- If QTcF greater than 500 ms: hold vandetanib
- Restart medication when QTc is less than 450 ms

Figure 1a. Contraindications/warnings in conjunction with vandetanib administration.

Figure 1b. Monitoring objectives, while receiving vandetanib.

All information taken from http://www1.astrazeneca-us.com/pi/vandetanib.pdf

**Vandetanib in Clinical Practice**

As seen in these trials vandetanib can increase progression free survival and decrease biochemical markers, but also has potentially life threatening side effects. In a recent meta-analysis involving patients with advanced solid tumors on VEGFR TKI’s (sorafenib, sunitinib, pazopanib and vandetanib) there was 1.64 fold increase in the risk of fatal adverse events in patients receiving the targeted agent [24]. There was no increased risk of venous thromboembolic events [25]. The four most common and serious side effects of vandetanib observed in meta-analyses include rash, diarrhea, hypertension, and QTc prolongation. Three different meta-
analyses of vandetanib alone demonstrated a 2.07–2.43 increased risk of rash over control [26–28]. There was a 1.59–1.64 fold increased risk of diarrhea compared to control with the use of vandetanib [26, 27]. Two meta-analyses found an increased risk of hypertension ranging from a 4.08 to 5.1 fold increased risk [26, 29].

The most serious and potentially fatal complication of vandetanib use was a 7.26–17.77 fold increased risk of QTc prolongation. The use of vandetanib in patients with congenital long QT syndrome is contraindicated (Figure 1a, 1b). Close monitoring of the QTc along with serum chemistries is needed at baseline and throughout treatment (Figure 1a, 1b). Before initiation of vandetanib, all electrolyte abnormalities should be corrected. Other QTc prolonging medications should be discontinued. ECGs should be obtained to monitor the QT at baseline, at 2–4 weeks and 8-12 weeks after starting treatment with vandetanib and then every 3 months while on the medication or if there is a dose adjustment (http://www1.astrazeneca-us.com/pi/vandetanib.pdf, Figure 1b). Warnings in patients with renal failure and uncompensated heart failure among other things need to be taken into account as demonstrated in Figure 1a.

Diarrhea is another potential side effect of vandetanib that, although less deadly, remains significant. It is difficult to determine whether the diarrhea experienced in trials was related to the drug or the malignancy since patients with MTC often experience diarrhea secondary to hypersecretion of calcitonin. In the phase III (ZETA) trial, there was a significant reduction in calcitonin levels but diarrhea continued to be an adverse event. However, what is not captured is whether there was a decrease in the frequency of the diarrhea since only the most significant episode of diarrhea is reported [30]. In cases of severe diarrhea the manufacturer recommends discontinuation of the drug until the diarrhea subsides. In patients with diarrhea, serum electrolytes and ECGs should be more carefully monitored given the increased risk of prolonged QTc with electrolyte instability. Patients with diarrhea should be closely monitored for potential dehydration and receive intravenous hydration as necessary.

Skin reactions are mostly described as sun sensitivity or mild to moderate rash, but there have been reports of severe reactions such as Steven Johnson's syndrome [31] with the use of vandetanib. In mild to moderate cases, topical or systemic corticosteroids and/or antibiotics are necessary. In cases of grade 3 or greater skin toxicity the medication should be held until symptoms resolve and restarted at a reduced dose. Deliberate attention to any skin changes at each follow-up appointment is indicated. The use of sun-protective clothing and sunscreen during administration and for 4 months after discontinuation is advised (http://www1.astrazeneca-us.com/pi/vandetanib.pdf).

Hypothyroidism has been an issue, with 49% of patients requiring increased thyroid replacement and has been seen in other TKI's as well [23, 32]. Other rare toxicities include interstitial lung disease, ischemic cerebral vascular events, serious hemorrhagic events, heart failure, and reversible leukoencephalopathy.

With findings suggesting overall increased rate of significant adverse events, including death, in patients receiving VEGFR inhibitors and black box warning of prolonged QT interval in vandetanib, careful patient selection, dosing and monitoring is needed for its use secondary to the potential serious complications, vandetanib can only be prescribed through the Risk Evaluation and Mitigation Strategy (REMS) program.

The optimal timing for the use of vandetanib is still unclear. In the phase III ZETA trial, there was a significant difference in the primary endpoint, progression free survival. Median duration of response was not reached at 24 months and significant reductions were seen in calcitonin and carcinoembryonic antigen [33]. Although these are impressive findings, it is not clear yet that this will translate into improved overall survival and improved quality of life given the significant side effects we have described above. Advanced or metastatic disease in MTC can often follow an indolent course and the benefit of prolonged administration of vandetanib in asymptomatic disease may not outweigh the potential risk. Appropriate selection of patients for vandetanib such as those with symptomatic disease, high disease burden, or rapidly progressive disease is vital in balancing progression free survival with health related quality of life and side effect risk.

**Conclusion**

The approval of targeted agents in the treatment of metastatic or advanced MTC is changing the treatment landscape of this disease. The approval of not only
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vandetanib in 2011 but cabozantinib, a TKI and VEGFR2 inhibitor, in 2012 provides additional therapeutic options in a disease not usually responsive to traditional cytotoxic therapy. Although vandetanib demonstrated promising progression free survival benefit as well as significant reduction in MTC associated biomarkers, the potential morbidity and mortality requires careful selection of which patients will truly benefit from treatment. Patients who have minimal symptoms from the malignancy may get little benefit or may incur harm from this medication. Therefore careful weighing of risk versus benefit is necessary to determine appropriate candidates for this treatment. Based on safety and efficacy information currently available we suggest that patients with an ECOG performance status of 0 and 1 be considered for treatment with vandetanib with select patients with an ECOG performance status of 2 being considered if individual practitioners feel that treatment would improve performance status. Given the lack of overall survival data, indolent course in some patients, and potential for toxicity, patients with minimal symptoms or those with a detectable calcitonin or slightly rising calcitonin level could be observed without treatment. Patients who are likely to benefit from vandetanib treatment have well-defined macroscopic disease with evidence of rapid calcitonin doubling time of less than 2 years [34]. Finally, we encourage all practitioners to enroll these patients on clinical trials so we may further characterize the efficacy, optimal timing for delivery and safety of vandetanib.

Disclosure

There are no conflicts of interest.

References

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