Vandetanib for aggressive and symptomatic medullary thyroid cancer

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Practice Points

- Medullary thyroid cancer is a disease characterized by mutations in the proto-oncogene *RET*.
- Vandetanib is a receptor tyrosine kinase inhibitor of RET, EGF receptor and VEGF receptor.
- Phase II and III studies have shown an improvement in progression-free survival in patients treated with vandetanib.
- Future studies should concentrate on overcoming resistance, improvement of side effects and efficacy, as well as an estimate of cost–effectiveness of vandetanib.

SUMMARY Medullary thyroid cancer accounts for less than 10% of all thyroid cancers. Aggressive metastatic forms of this disease however, are incurable and can cause significant symptoms including diarrhea and pain. Hereditary and some sporadic forms of the disease are characterized by a mutation of the proto-oncogene RET. This results in an abnormal growth factor receptor that, in turn, allows the malignant cells to survive and metastasize. New tyrosine kinase inhibitors have been shown to effectively target RET *in vitro*. One of the first of these agents, vandetanib, has been evaluated in international Phase II and III clinical trials. In 2011, vandetanib became the first agent approved by the US FDA for use in metastatic medullary thyroid cancer. This article examines the clinical use of this agent.

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Medullary thyroid cancer (MTC) was first described in the 1950s [1], and accounts for less than 10% of the 56,460 estimated new cases per year of thyroid cancer [2]. Unlike differentiated forms of thyroid cancer, MTC is not associated with radiation exposure and arises from parafollicular or C cells [3]. Multiple hereditary forms of this disease have since been described, including familial MTC (FMTC) and the multiple endocrine neoplasia syndromes (MEN 2A and MEN 2B) [4–7]. Although the familial syndrome and association with other endocrinopathies including pheochromocytomas and primary hyperparathyroidism [8] have been extensively researched over the last 50 years, sporadic MTC remains the most common variant. MTC differs from many solid tumors in that it has reliable tumor markers (calcitonin and carcinoembryonic antigen [CEA]) that can effectively be used to help manage the disease. Both are used in clinical practice and also in clinical trials to determine response to treatment. The present authors however, caution against using results of a blood test as the sole reason for treatment, as will be discussed later in the review [9].

Multivariate analysis has shown stage to be the predominant factor for survival in MTC (Box 1). Prior studies have shown the survival for patients requiring systemic therapy to be 6–22 months [10]. Review of the Surveillance, Epidemiology and End Results (SEER) database of over 1200 cases of the disease, demonstrated a mean survival time after the diagnosis of MTC of 8.6 years (range: 0–29.6 years). Patients with tumors confined to the thyroid gland had a 10-year survival rate of 95.6%, whereas patients with regional stage disease had an overall survival rate of 75.5%. Patients with distant metastases at diagnosis had a poor prognosis, with only 40% surviving 10 years and an overall survival of approximately 36 months [11]. Chemotherapy agents have been tried with limited success. Early studies focused on doxorubicin alone or in combination with cisplatin, although later reports have shown activity using derivatives of fluorouracil [12–14]. In general, early studies were limited by toxicity and a lack of efficacy.

Box 1. Prognostic factors in medullary thyroid cancer.

- Age
- Stage
- Clinical course
- Persistent diarrhea
- Metastasis and compression of adjacent tissue
- Calcitonin doubling in less than 1 year
- Presence of *RET* mutations

Use of external beam radiation therapy may aid in locoregional control of metastatic disease, but does not prolong survival [15]. Occasional cases have been described where successful therapy to control metastatic disease has been provided with ^{131}I-meta-iodobenzylguanidine, to which a subset of MTC tumors are responsive [16].

Targeted therapy for MTC

Subsequent advances in drug development have led to the synthesis of many new targeted agents that are inhibitors of specific growth factors or cell signaling pathways involved in the pathogenesis of many solid tumors including MTC [17].

Mutations in specific regions of *RET* proto-oncogene have been described in patients with both familial and sporadic forms of MTC. It has also been demonstrated that the presence of a somatic *RET* mutation correlates with a worse outcome for MTC patients; both for persistence of the disease and also for a lower survival rate in a long-term follow up. The presence of a somatic *RET* mutation correlates with the presence of lymph node metastases at diagnosis, which is known to be a poor prognostic factor for the definitive cure of MTC patients [18]. RET therefore represented an obvious target for specific drugs to treat unresectable forms of the disease.

Many cancers also rely on angiogenesis or the formation of new blood vessels to enable growth of the primary tumor and metastasis to distant sites. Angiogenesis appears to be controlled by a variety of proteins including the VEGF proteins and specific VEGF receptors (VEGFRs) on the cell surface. Vandetanib targets both RET and VEGFR and will be described in detail in this article.

RET proto-oncogene

RET was first discovered in patients with MEN syndromes [19], although it was not until 1985, that a new human transforming gene was detected by transfection of NIH 3T3 cells with lymphoma DNA [20]. Subsequent work pinpointed mutations on chromosome 10, followed by the identification of germline mutations in the *RET* proto-oncogene, located at 10q11.2 in patients with MEN 2A, MEN 2B and FMTC [21,22].

RET is now thought to be one of a number of important receptor tyrosine kinases (RTKs) that are present on cancer cells. These glycoproteins, including RET, receive extracellular signals resulting in activation of growth factor pathways, causing processes as diverse as cell growth, differentiation, survival and programmed cell death (Figure 1). In response to binding of extracellular ligands, RTKs generally form homodimers or heterodimers. In the case of RET, the glial cell line-derived family of ligands and the glycosylphosphatidylinositol-anchored glial cell line-derived family α-receptors appear to be the most important for activation. Potential targets for inhibition of RET-associated malignancies include antibody inhibition of the ligand binding site, enzymatic inhibition of the RTK and downstream inhibition of targets in the signal transduction cascades [23]. Vandetanib is an inhibitor of the RTK.

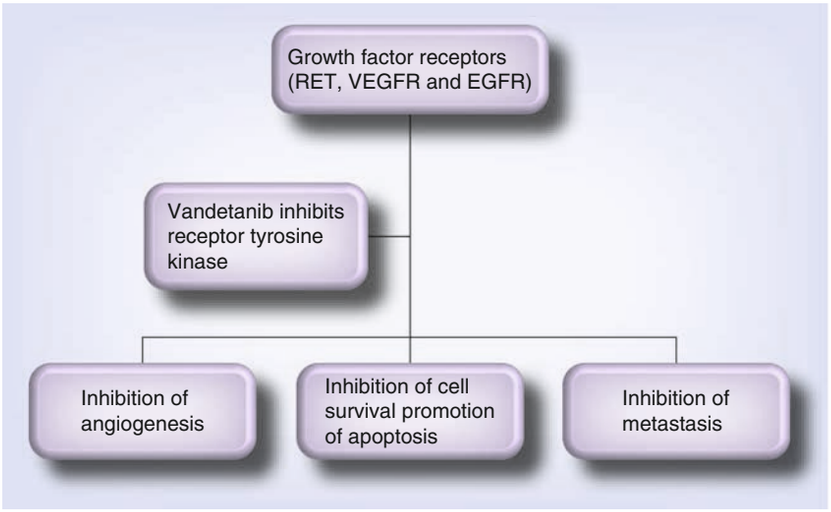

Figure 1. Transmembrane growth factors and the mechanism of action of vandetanib.
EGFR: EGF receptor; VEGFR: VEGF receptor.

The VEGFR pathway

The VEGFR pathway is also important in the pathogenesis of MTC [24]. This too has been extensively studied and, like RET, involves activation of a RTK followed by activation of a downstream signal transduction cascade, resulting in proliferation and invasion of malignant cells [25].

Vandetanib

Vandetanib (*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl) methoxy]quinazolin-4-amine) was developed by AstraZeneca under the name ZD6474, and was later called vandetanib, Zactima and finally Caprelsa™. It is an oral compound with a bioavailability of >50%. It competes with ATP binding in the catalytic domain of several tyrosine kinases including RET, VEGFR2, VEGFR 3 and EGF receptors. This inhibition resulted in inhibition of VEGF-stimulated endothelial stimulation, inhibition of tumor cell growth and inhibition of tumor angiogenesis in preclinical models [26–28]. This profile made it an attractive choice for further studies of MTC.

Phase I studies

Two Phase I dose-escalation studies evaluating daily vandetanib alone in advanced solid tumors were completed. The first was conducted in the USA and Australia. This study enrolled 77 patients with a variety of tumor types in a dose-escalation clinical trial [29]. Dose-limiting toxicities included diarrhea, hypertension and rash, and from the toxicity experienced in this study, the recommended dose to evaluate in further studies was determined to be 300 mg daily. This dose was well tolerated. Asymptomatic QTc prolongation was also observed in seven patients. Pharmacokinetic studies showed vandetanib to be extensively distributed, with a half-life of approximately 120 h and a minimum of 28 days continuous oral dosing required to achieve steady-state plasma concentrations. The second Phase I study was conducted in Japan, enrolling 18 patients [30]. This study yielded similar findings and once again 300 mg was the recommended Phase II dose.

Studies involving vandetanib & MTC

■ Single-arm Phase II studies

Initially it was determined that the most efficacious use of vandetanib would be in patients with germline mutations of RET, as this represented one of the primary targets of the drug. Therefore, patients with unresectable, locally advanced or metastatic MTC with a confirmed clinical diagnosis of MEN2A, MEN2B or FMTC and a germline RET mutation were eligible for a study using this agent at an initial dose of 300 mg daily [31]. Patients had to have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, WHO performance status of 0–2 and adequate cardiac, hematopoietic, hepatic and renal function. This

was an open-label, Phase II study conducted at seven centers. Patients received once-daily oral doses of vandetanib 300 mg until disease progression, unacceptable toxicity or withdrawal of consent occurred. The primary end point was objective response by RECIST. Additional assessments included the duration of response, disease control, progression-free survival (PFS), safety and tolerability, and changes in the serum levels of polypeptide, calcitonin and CEA secreted by MTC cells. Between November 2004 and August 2006, a total of 30 patients were enrolled. At the time of data cutoff (22 February 2008), seventeen patients were still continuing treatment. Four had disease progression by RECIST measurements but were receiving clinical benefits and allowed to remain on study. The remaining patients discontinued vandetanib because of adverse events (n = 7) disease progression (n = 4) or withdrawal of consent (n = 2). The majority of patients had MEN2A and 29 of the 30 had evidence of metastatic disease at presentation. A total of 20% of subjects (six patients) achieved a partial response, and another 53% had stable disease for more than 24 weeks. The median duration of response was 10.2 months (range: 1.9–16.9 months; CI: 8–13.2 months). The majority of patients (80%) had reductions in their calcitonin levels to less than half the baseline values for at least 4 weeks [31].

The eligibility criteria was similar in a second Phase II study using a lower dose of the drug (100 mg) as monotherapy in patients with locally advanced or metastatic familial forms of MTC [32]. The primary objective was again to assess the objective response rate with vandetanib according to RECIST criteria. Upon disease progression however, all patients that the investigator believed may have been obtaining clinical benefit from therapy could enter postprogression treatment with vandetanib 300 mg/day until objective disease progression occurred at this dose, or until another withdrawal criterion was met. A total of 19 patients were recruited between August 2006 and May 2007, all initially receiving 100 mg daily. At the time of data cutoff 11 were continuing on this dose and the rest had discontinued initial treatment. Four of these had disease progression, and all entered postprogression treatment with vandetanib 300 mg daily. There were no complete responses, 3 (16%) partial responders and 10 patients had stable disease for 24 weeks or longer. In this study, disease control was seen in 68% of all patients (including complete and partial responders and those who had stable disease for greater than 24 weeks). Toxicities were manageable in both trials, with the most common adverse events being diarrhea, rash and asymptomatic QTc prolongation on ECG [32]. Although it could be seen from both trials that 100 mg daily and 300 mg daily of vandetanib each had activity in this disease, no direct comparison of these dose levels has been conducted. The level chosen for the randomized placebo-controlled study was 300 mg daily.

Randomized Phase III study

The encouraging results of these single-arm trials spurred accrual onto an international randomized, double-blind Phase III trial (known as the ZETA trial) comparing ZD6474 to placebo in patients with inherited and sporadic forms of MTC [33]. In this large trial, 331 adults with unresectable locally advanced or metastatic MTC were randomized in a 2:1 manner to receive either ZD6474 (vandetanib) at a dose of 300 mg daily or placebo, respectively. Between December 2006 and November 2007, 231 subjects were assigned vandetanib and 100 received placebo. The majority of patients had sporadic disease (90%), metastatic stage (95%) and tumors that were positive for a RET mutation (56%). Patients were followed until disease progression, at which time they were unblinded and had the option to receive vandetanib in an open-label trial; if they chose open-label vandetanib, they were then followed for survival. The median duration of treatment was 90.1 weeks in the vandetanib arm and 39.9 weeks in the placebo arm. The primary objective of the ZETA study was demonstration of improvement in PFS with vandetanib compared with placebo. Other end points included evaluation of overall survival and objective response rate.

The 2-year follow-up results showed that 37% of the patients had progression and 15% had died. The primary end point of the study, PFS, was met with the researchers reporting a hazard ratio (HR) of 0.46 (95% CI: 0.31–0.69). The median PFS was 19.3 months in the placebo group and had not yet been reached in the vandetanib arm at the time of presentation at the 14th International Thyroid Congress in 2010. A significant improvement in PFS was observed

for patients randomized to receive vandetanib (HR: 0.35; 95% CI: 0.24–0.53; p < 0.0001). While the PFS data led to FDA approval, no significant overall survival difference was noted in the two arms because of the crossover design of the study. Vandetanib was also associated with statistically significant advantages in secondary end points such as objective response rate (45 vs 13%; odds ratio [OR]: 5.4); disease control rate of 24 weeks or more (OR: 2.64); calcitonin biochemical response (OR: 72.9); CEA biochemical response (OR: 52); and time to worsening of pain (HR: 0.61). Some of the radiological responses were dramatic. At this time it is not known whether any biochemical, radiological or clinical parameters significantly predict for response. Similarly, data is not yet available on whether certain metastatic sites respond better than others. In the placebo arm, 12 of 13 responses occurred after the patients had received open-label vandetanib. Adverse events were more common with vandetanib compared with placebo, including diarrhea (56 vs 26%), rash (45 vs 11%), nausea (33 vs 16%), hypertension (32 vs 5%) and headache (26 vs 9%). The most severe toxicity was QT prolongation, *torsades de pointes* and sudden death, which are addressed in a boxed warning in the prescribing information. A summary of the results of the Phase II and III trials is shown in **Table 1**.

Based on these results, AstraZeneca filed for FDA approval of the drug in the USA and the EMEA approval in Europe in late 2010, receiving an orphan drug designation by the FDA on 2 December 2010, with final approval granted on 6 April 2011 [101]. The approval was specifically for patients who are ineligible for surgery and have disease that is growing or causing symptoms. The benefits of the drug on patients who have occult or micrometastatic disease but with a rapid calcitonin doubling time are not known.

A meta-analysis of trials using vandetanib in all cancer patients found the incidence of all grade and high-grade hypertension to be 24.2 and 6.4%, respectively. In patients specifically with MTC receiving vandetanib, the incidences were 32.1% for all grade hypertension and 8.8% for high-grade hypertension. Furthermore, patients with MTC who had longer treatment durations also had a higher incidence of all-grade events than patients with lung cancer or other cancers [34]. Investigators have also shown that toxicities, including QTc prolongation may be more common in patients with lower mean muscular mass (37 vs 44 cm^2/m^2), suggesting that these subjects should be monitored more frequently than the generally accepted follow-up schedule of every 1–3 months. [35]

The severe cardiac side effects mentioned above are addressed in a boxed warning in the prescribing information. Vandetanib has a prolonged half-life of 19 days, therefore, ECGs and levels of serum potassium, calcium, magnesium and TSH should be obtained at baseline, at 2–4 and 8–12 weeks after starting treatment and every 3 months subsequently. As a result of the FDA concern about toxicity, only US prescribers and pharmacies certified through the vandetanib risk evaluation mitigation strategy program, a restricted distribution program, are able to prescribe and dispense vandetanib.

Conclusion

The approval of vandetanib as a systemic treatment for patients with unresectable or metastatic MTC was a landmark event and represents a new standard of care for these patients. However, it does not mean that everyone with metastatic MTC should take this medication. It must be remembered that, like most systemic treatments for metastatic cancers, this does not represent a cure for the disease. Careful patient selection must be used when deciding to use this medication. MTC has a 40% 10-year survival even for patients with metastatic disease – from data that was obtained before vandetanib was available [9]. Therefore, many patients, especially the asymptomatic ones with slow growing or relatively stable disease should not be offered systemic anti-neoplastic therapy unless one exists with a clear survival benefit and no or minimal

Table 1. Studies using vandetanib for medullary thyroid cancer.

Study (year)	Phase	Dose of vandetanib (mg)	Number of patients	Partial/overall response rate (%)	Ref.
Holden *et al.* (2005)	II	300	30	20	[29]
Tamura *et al.* (2006)	II	100	16	16	[30]
Wells *et al.* (2010)	III	300	331	45	[31]

side effects. Further improvements in PFS and overall survival however, are considered possible and may be achieved with combination therapy using vandetanib and either chemotherapy agents or other targeted treatments, especially for patients with aggressive, rapidly progressing disease. Furthermore in our increasingly healthcare–cost conscious society, it is likely that the high cost of a new tyrosine kinase inhibitors such as vandetanib is also likely to limit the number of patients who may have access to this medication.

If these concerns are addressed then there is a role for vandetanib in the treatment of aggressive metastatic MTC treatment. Care must be taken to screen patients for cardiac histories. Furthermore, clinical trials accept only a select group of patients who fit stringent eligibility criteria. Such patients may not be representative of the general population of patients suffering from the disease. One study however, evaluated the use of tyrosine kinase inhibitors in patients receiving off-label therapy for refractory thyroid cancers. Of these, 14 had MTC treated with vandetanib. In these patients, the partial response rate was 36% and median PFS was 39.1 months, suggesting a similar effect to that seen in the large randomized trial [36].

Future perspective: the clinical utility of vandetanib

Resistance may arise in tumors exposed to vandetanib. The present authors speculate that there may be many reasons for this including new molecular abnormalities involving RET or other receptors such as loss of expression, genomic amplification or the activation of alternative downstream signaling pathways. Further work needs to be done to elucidate which of these is most important. The combination of vandetanib and other drugs may help delay or overcome some resistance mechanisms. It appears to be safe and effective when combined with the proteosome inhibitor bortezomib in a small Phase I/II study, with 29% of patients achieving a partial response and 47% stable disease [37].

Vandetanib has been tried in many other malignancies with varying success rates [38–39]. If it is approved for use in more common cancers such as lung or breast cancer, then added experience with the agent may allow different dosing schedules and combinations to be tried. This, in turn, may benefit patients with MTC who are unable to tolerate the recommended dosing of vandetanib.

Healthcare reform and cost-effective treatments became heavily debated political topics in the early 2000s. Cost-effective research is a controversial area that is being addressed with a National Comparative Effectiveness Research institute [40]. Many new treatments for more common cancers have come under scrutiny because of their cost. Sipeleucel-T (Provenge®, Dendreon, WA, USA) became the first vaccine therapy to be approved for cancer treatment in 2010. It is an autologous dendritic cell treatment used in the treatment of minimally symptomatic castration-resistant prostate cancer. In Phase III clinical trials, it resulted in an improvement in survival of approximately 4 months compared with best supportive care [41]. The cost to Medicare patients in the USA is approximately $93,000 for the course of three infusions [42]. Arguments for this high price tag include the preparation of the medication including extraction of dendritic cells on three occasions, transportation of the sample and the manufacture of an individual vaccine in the only Dendreon processing plant currently located in New Jersey, USA. Other medications have a similarly high cost. Abiraterone (Zytiga®, Janssen, NJ, USA), a hormonal treatment for metastatic castration-resistant prostate cancer, is expected to cost approximately US$5000 dollars a month and resulted in an average survival of approximately 15 months – a total cost of US$75,000 [43]. Vandetanib, like many tyrosine kinase inhibitors, is expected to cost approximately US$10,000 for a 30-day supply [44]. The improvement in survival seen in the ZETA trial suggests that patients receiving this medication may be on treatment for in excess of 30 months. It is not clear whether vandetanib can be used effectively in a maintenance or intermittent schedule, which would reduce costs significantly. Patient selection is important when using this medication as many patients with metastatic MTC remain asymptomatic and often productive members of society. For more symptomatic patients, a reduction of disease burden may allow them to return to work and offset the economic deficit caused by the high cost of treatment. Future economic models may be able to more accurately predict the true cost of the drug when more experience with it has been established.

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