Vandetanib for the Treatment of Medullary Thyroid Cancer

Nicole G. Chau and Robert I. Haddad

Abstract

Vandetanib (ZD6474, Caprelsa, AstraZeneca), an oral small-molecule tyrosine kinase inhibitor (TKI) that targets the rearranged during transfection receptor (RET), VEGF receptor (VEGFR2-3), and EGF receptor (EGFR), is the first systemic therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of symptomatic or progressive advanced medullary thyroid cancer (MTC). In a randomized phase III trial of patients with unresectable, locally advanced, or metastatic MTC, vandetanib improved progression-free survival compared with placebo [HR, 0.46; 95% confidence interval (CI), 0.31–0.69; P < 0.001]. However, the benefits in delaying disease progression need to be balanced against the associated and potentially serious toxicities, including diarrhea, hypertension, and QTc prolongation. Here, we review the clinical development of vandetanib leading to its integration into the current treatment paradigm and highlight the ongoing and future challenges in TKI use in MTC. Clin Cancer Res; 19(3); 1–6. ©2012 AACR.
Vandetanib showed efficacy in all evaluable endpoints in the ZETA trial except survival. At a median follow-up of 24 months, median PFS was not reached with vandetanib (estimated ~30 months) and was 19.3 months with placebo [HR, 0.46; 95% confidence interval (CI), 0.31–0.69; P < 0.001; ref. 15]. The 6-month PFS rate was 83% in the vandetanib group and 63% in the placebo group. Vandetanib showed a higher ORR than placebo (45% vs. 13%; P < 0.001) and higher DCR (87% vs. 71%; P = 0.001). Of the 13 patients in the placebo arm who responded, 12 did so after treatment with open-label vandetanib. Overall survival data were immature at the time of analysis and revealed no significant difference (HR, 0.89; 95% CI, 0.48–1.65). Final survival assessment is likely to be confounded by post-progression cross over from placebo to open-label vandetanib. The biochemical response rate (complete response defined as normalization of serum levels; partial response defined as ≥50% decrease from baseline in serum calcitonin and CEA for ≥4 weeks) was better for vandetanib than for placebo (69% vs. 3% for calcitonin; P < 0.0001; 52% vs. 2% for CEA; P < 0.0001). Vandetanib was associated with a delay in time to worsening of pain (HR, 0.61; 95% CI, 0.43–0.87; P = 0.006); however, other health-related quality-of-life measures were not evaluated.

**Efficacy**

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**Efficacy by mutation status**

A tremendous effort was made to correlate RET genotype with response to vandetanib in the ZETA trial. Tissue was obtained for RET genotyping in 297 of 298 patients with sporadic MTC. Somatic RET mutations were identified in 155 patients (52%), and somatic RET mutations were absent in 8 patients (2.7%; ref. 15). Unfortunately, a large proportion of patients was classified as RET mutation status “unknown” (n = 135; 45.3%) due to insufficient tumor DNA to fulfill stringent testing criteria, making subgroup analysis by RET mutation status for PFS and ORR in ZETA inconclusive. Interestingly, patients with sporadic MTC tumors harboring a somatic M198T mutation had a higher response rate to vandetanib (54.5%; 55 of 101) than patients with sporadic MTC tumors without a somatic M918T mutation (32%; 33 of 103). Vandetanib appeared active in all prespecified subgroups (16).

**Safety and tolerability**

The most common and serious adverse events in ZETA are listed in Table 2. Vandetanib was associated with higher treatment discontinuation rate (12% vs. 3%) and dose reductions due to adverse events or QTc prolongation (36% vs. 3%) compared with placebo (15). However, median duration of treatment was much longer for vandetanib (90.1 vs. 39.9 weeks). Vandetanib at 300 mg/d was associated with QTc prolongation (mean, 35 ms) but there were no reports of torsades de pointes in ZETA.

**Integration of Vandetanib into the Medullary Thyroid Cancer Treatment Paradigm**

Few treatment options exist for patients with unresectable or metastatic MTC. In metastatic disease, a watch-and-wait approach is feasible in asymptomatic patients with low tumor burden, and no evidence of tumor progression on
periodic restaging as patients with indolent metastatic disease may survive for years without systemic therapy. For patients with progressive or symptomatic metastatic disease and high tumor burden, the National Comprehensive Cancer Network (NCCN) encourages clinical trial enrollment. In the absence of trial enrollment, systemic therapy with TKIs is preferred over cytotoxic chemotherapy, which is associated with high toxicity and low efficacy. Vandetanib is currently the first-line systemic therapy of choice. If a patient is not a candidate for vandetanib or progresses on vandetanib, NCCN guidelines recommend the use of commercially available TKIs such as sorafenib or sunitinib, although these agents are not FDA approved for the treatment of thyroid cancer and their phase II trials specifically excluded patients with prior vandetanib therapy (2, 3).

In practice, deciding when to initiate vandetanib therapy is less clear. The use of vandetanib should be restricted to symptomatic or rapidly progressive MTC, which is determined by clinical judgment as neither were part of the ZETA inclusion criteria. No validated predictors of response to vandetanib exist to guide patient selection. Subgroup analyses suggest that there may be a greater chance of benefit in patients with sporadic MTC tumors harboring the aggressive M918T mutation and in patients with CEA doubling times ≤24 months compared with those with longer doubling times (54% vs. 37%; ref. 16). Judicious evaluation of the treatment risk-to-benefit ratio and close monitoring for toxicities is critical. Because of the potential of QT prolongation, torsades de pointes, and sudden death, vandetanib is currently only available through the FDA Vandetanib Risk Evaluation Mitigation Strategy (REMS) Program. The goal of the program is to educate prescribers about the risk, appropriate monitoring, and management of QT prolongation and to minimize the occurrence of torsades de pointes and sudden death associated with vandetanib. To prescribe vandetanib, providers must complete provider training and enroll in the vandetanib REMS program. ECG and serum potassium, calcium, magnesium, and thyroid-stimulating hormone levels should be closely monitored and corrected. Concomitant use of drugs that prolong the QT interval or are associated with torsades de pointes should be avoided, recognizing that the risk for torsades de pointes may be protracted given the drug’s long half-life (t1/2 = 19 days). Other common side effects (Table 2) including diarrhea, rash, and hypertension can usually be managed with early recognition, supportive measures, and dose reductions or interruptions for grade ≥III severity (17). Most patients treated with vandetanib will have an increase in thyroid-stimulating hormone levels compared with baseline (11). In the ZETA trial (15), thyroid-stimulating hormone levels increased from baseline in 42% of patients treated with vandetanib, compared with 8% of placebo-treated patients. The mechanism of action of vandetanib is believed to include inhibition of type III TSH receptor, which may account for this finding.}

### Table 2. Summary of common adverse events occurring with an incidence of ≥25% and grade III+ adverse events occurring with an incidence of ≥5% on either arm in phase III trials in advanced MTC

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<td><strong>ZETA Trial (15)</strong></td>
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<td><strong>Vandetanib</strong> (n = 231)</td>
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stimulating hormone (78%) and about 50% will require increases in thyroid replacement dose. Given the toxicity profile, vandetanib is clearly unjustified for asymptomatic, indolent disease.

The MTC treatment schema is quickly evolving as clinical trials inform on new therapies. Cabozantinib, an oral kinase inhibitor of VEGFR2, RET, and hepatocyte growth factor receptor (MET), is the only other TKI with randomized phase III data (EXAM trial) in progressive, advanced MTC showing a PFS benefit (primary endpoint) compared with placebo (median PFS = 11.2 vs. 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; \( P < 0.0001 \)) and an ORR of 28% versus 0% (18). Unlike ZETA, the EXAM trial eligibility criteria included disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) within 14 months of screening. Similar to ZETA, very few patients were considered RET mutation negative, thus subgroup analysis by RET mutation status for PFS was inconclusive. Toxicities associated with VEGF inhibition led to deaths in 1.9% of patients in the cabozantinib arm (3 cases of fistula formation and 1 hemorrhage; ref. 18). In the future, cabozantinib may be an alternative first-line treatment option to vandetanib, particularly for patients with rapidly progressive disease or high risk for torsades de pointes, or cabozantinib may be a second-line option postprogression after vandetanib; however, the toxicities related to VEGF inhibition must be weighed (Table 2). Future trials of head-to-head upfront comparison of TKIs and sequential approaches are needed to inform. Uncertainty exists about the optimal treatment strategy when resistance to TKI therapy develops. It is unclear how many patients in the ZETA trial received prior TKIs. In the EXAM trial, about 20% of patients had received prior TKI therapy and response was seen regardless of prior TKI treatment. Evidence to support the use of sorafenib or sunitinib after vandetanib progression is largely anecdotal.

Future Challenges

Vandetanib represents a paradigm shift in the treatment of MTC by validating the efficacy of TKIs in advanced MTC.
However, challenges remain in optimizing patient selection, mitigating treatment toxicities, and identifying strategies to overcome resistance as these therapies are currently not curative. Mechanisms of primary and acquired resistance to vandetanib require investigation. Presently, RET mutations cannot be used clinically to predict response to TKIs, although correlations may be strengthened in the future as TKI use and genetic testing in sporadic MTC increases. Comparison of sequential tumor biopsies pre/posttreatment and upon resistance may provide insight into clinical mechanisms of resistance.

Characterization of antitumor activity of vandetanib and other TKIs against specific RET mutant and RET wild-type tumors may help to better select patients for therapy. ZETA confirms the clinical efficacy of vandetanib in patients with sporadic MTC tumors harboring the M918T mutation. Prior studies hinted that somatic M918T mutations may confer sensitivity to RET TKIs; in patients with somatic M918T mutations, 12 of 15 had durable responses or stable disease in the phase I trial of cabozantinib (7) and 5 of 8 patients had responses to sunitinib (3). However, the clinical efficacy of vandetanib in patients harboring other RET mutations such as those associated with MEN2A is less apparent. In vitro studies comparing the activity of 4 TKIs (vandetanib, axitinib, sunitinib, and cabozantinib) in MEN2B, MEN2A, and RET/PTC1 (papillary thyroid cancer) cell lines reported that vandetanib was the most potent inhibitor in MEN2B and cabozantinib was the most effective in MEN2A and PTC1 (19), suggesting that mutation-specific therapies may be beneficial. In addition, to avoid maleficence, identification of a subset of patients for whom vandetanib therapy is futile is important. For example, in vitro studies pinpointed that the RET V804M and V804L gatekeeper mutations confer resistance to vandetanib (20). Although rare, these mutations occur in sporadic and hereditary MTC, either alone or in combination with other RET mutations, and thus could result clinically in primary or acquired resistance to vandetanib. TKIs such as sorafenib have shown activity against the V804 mutant in in vitro studies (21). Finally, in patients with RET wild-type tumors, it remains to be seen whether Ras mutations, identified in 60% to 80% of RET-negative sporadic MTC (22), confer clinical resistance to vandetanib. In vitro studies using cell lines with acquired resistance to vandetanib have shown persistent activation of the Ras/Raf/MEK pathway, which can be partly abrogated by sorafenib (23).

Ultimately it remains unclear whether the activity of vandetanib is predominantly due to inhibition of RET, EGFR, VEGFR, or other kinases. For example, dual inhibition of RET and EGFR may contribute to the efficacy of vandetanib (24); however, EGFR inhibition alone with gefitinib has not produced clinical responses in MTC (25). All clinically tested RET inhibitors are nonselective, multikinase inhibitors that also inhibit VEGFR signaling; however, VEGFR inhibition alone (axitinib) has shown a response rate less than 20% (5). The clinical efficacy of targeting VEGFR without RET inhibition is being evaluated in MTC in a single-arm phase II trial of pazopanib (GW786034, Votrient, GlaxoSmithKline; VEGFR1-3, PDGFRα/β, KIT inhibitor) in advanced thyroid cancer (NCT00625846). Interestingly, in a phase II trial of lenvatinib, there was no difference in treatment response according to RET mutation status; however, high baseline levels of VEGF and sVEGFR3 correlated with greater tumor shrinkage, and low levels of ANG2, sTie-2, HGF, and interleukin (IL)-8 were associated with tumor shrinkage and prolonged PFS (6). This distinction is important as the main serious adverse events associated with the current RET TKIs are related to anti-VEGFR or anti-EGFR effects. Greater understanding of the mechanism of activity of vandetanib will permit rational exploration of sequential or combination approaches with other therapies in the future including clinical development in the neoadjuvant or adjuvant setting.

Conclusions

Vandetanib showed clinical efficacy and PFS benefit in advanced MTC, thus validating small-molecule TKIs as a valid therapeutic strategy in this disease. However, the toxicities, some serious including QTc prolongation, need to be carefully weighed and managed. Vandetanib is unjustified in the setting of indolent and asymptomatic MTC. The risk–benefit assessment must take into account the toxicity risks, prolonged treatment administration, and potential indolent course of advanced MTC. The MTC treatment paradigm is rapidly changing, as future TKI studies continue to inform. Work is needed to further characterize appropriate patient selection, optimize management upon resistance, and examine novel sequential or combination treatment approaches.

Disclosure of Potential Conflicts of Interest

R.I. Haddad has a commercial research grant from Astra Zeneca and is a consultant/advisory board member for Exelixis. No potential conflicts of interest were disclosed by N.G. Chau.

Authors' Contributions

Conception and design: N.G. Chau, R.I. Haddad

Development of methodology: R.I. Haddad

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N.G. Chau

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N.G. Chau

Writing, review, and/or revision of the manuscript: N.G. Chau, R.I. Haddad

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References


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