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REVIEW

Vandetanib (ZD6474) in the Treatment of Medullary Thyroid Cancer

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Abstract: Vandetanib (ZD6474) is an orally bioavailable small molecule tyrosine kinase inhibitor of multiple growth factor receptors, including RET (Rearrange during transfection), vascular endothelial growth factor receptor-2 (VEGFR-2) and epidermal growth factor receptor (EGFR). The activity against RET and VEGF made it a good choice in the treatment of medullary thyroid cancer (MTC). As there is considerable cross talk between growth factor pathways, dual inhibition with such agents has become an attractive strategy, in the treatment of many malignancies with encouraging Phase II clinical trial data to date. Vandetanib was tested in two Phase II trials in the treatment of patients with medullary thyroid cancer at doses of 100 mg and 300 mg daily respectively. The encouraging results of these 2 trials led to a randomized phase II trial comparing this medication to placebo using a crossover design. More than 300 patients were included in this study, which ultimately showed a significant improvement in progression-free survival in patients taking vandetanib. Based on these results, the Oncology Drug Advisory Committee (ODAC) of the Food and Drug Administration (FDA) recommended that vandetanib be approved for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.

Keywords: Zactima, ZD6474, medullary thyroid cancer, vandetanib

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Introduction

Medullary thyroid cancer (MTC) accounts for fewer than 10% of all incident cases of thyroid malignancy but a disproportionately greater number (13.4%) of thyroid cancer-related deaths.[1] Radioiodine is ineffective in the treatment of this indolent malignancy, which originates from the parafollicular C cells that produce calcitonin, and not iodine-rich thyroid hormone. The pathogenesis of this disease has been extensively documented over the past 50 years. Soon after the earliest descriptions of this disease in 1959,[2] there were reports of a familial syndrome, initially in a single family[3] and subsequently associated with other disorders including pheochromocytomas and primary hyperparathyroidism.[4,5] It is now clear that there are multiple hereditary forms of this cancer, including familial MTC (FMTC) and the Multiple Endocrine Neoplasia Syndromes (MEN 2A and MEN 2B), although the sporadic form still constitutes the majority of the cases.[6] MEN 2A accounts for 60% of the hereditary forms, MEN 2B 5%, and FMTC 35%.[7]

Distant metastatic disease is the main cause of death in patients with MTC, occurring at presentation in approximately half of incident cases and often involving multiple organs such as the liver, lungs, and bones.[8] Extra-cervical metastases and unresectable advanced local disease are essentially incurable. Consequently, the best chance of curing patients with the disease is to identify patients at an early stage when the tumor is amenable to resection, especially if it is confined to the thyroid. In a review of over 1200 cases, the mean survival time after the diagnosis of MTC was 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.[9] Although traditional cytotoxic chemotherapy and radiation techniques have been historically ineffective in MTC, novel small molecule tyrosine kinase inhibitors appear to hold promise.[10]

Targeted Therapy

The explosion of targeted therapies in the field of medical oncology has given the potential for effective treatments for previously incurable diseases such as chronic myeloid leukemia.[11] A hallmark of MTC is the association with the rearranged during transfection proto-oncogene (RET) which as noted above, is involved in cell signalling, and regulation of the production of proteins that are essential for spermatogenesis and the development of the autonomic nervous system and kidneys. Mutations in specific regions of the RET gene have been described in MTC, and these occur in both the sporadic and familial forms of the disease.[12,13] These mutations have motivated experiments looking at corrective gene therapy as a treatment strategy.[14]

RET (Rearranged During Transfection) Proto-Oncogene

Until recently, it was likely that the detection of tumor at an early stage occurred either by the incidental finding of a thyroid nodule, or through screening of family members of an index patient who had previously been diagnosed with MTC or with the MEN 2 syndrome. Previous work had shown that the MEN syndromes are inherited in an autosomal dominant manner,[15] suggesting that 50% of patients would be screened unnecessarily. The yield from screening was improved with the discovery in 1985 of a new human transforming gene detected by transfection of NIH 3T3 cells with a lymphoma DNA.[16] Subsequent work pinpointed mutations on chromosome 10, followed by the identification of germline mutations in the RET (rearranged during transfection) proto-oncogene, located at 10q11.2, in patients with MEN 2A, MEN 2B, and FMTC.[6]

Receptor tyrosine kinases (RTK) including RET, receive the extracellular signals for processes as diverse as cell growth, differentiation, survival, and programmed cell death (Fig. 1). In response to binding of extracellular ligands, RTKs generally form homodimers or heterodimers. On dimerization, autophosphorylation occurs, followed by intracellular signal transduction through effectors that recognize and interact with the phosphorylated form of the RTK. Although the downstream signaling pathways activated by these steps may be shared by different receptors, the ligand-receptor interaction itself is very specific. In some cases, however, high-affinity ligand-RTK interactions can be modulated by the presence of other, low-affinity, nonsignaling accessory molecules at the cell surface.[12]

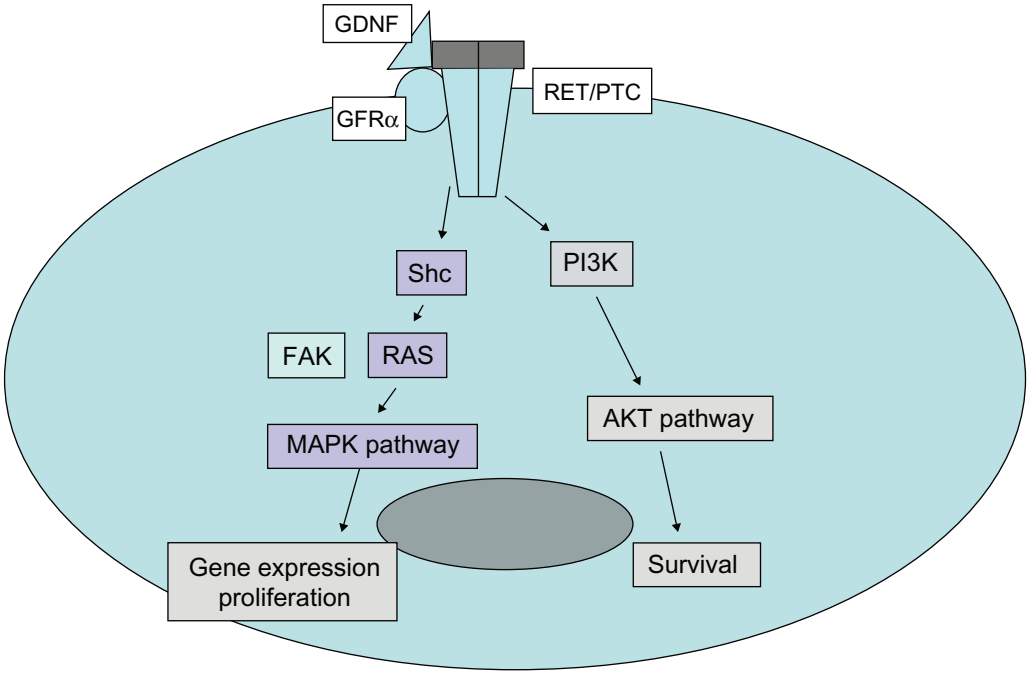

Figure 1. Interaction of ligand with RET and cell signaling pathways.
GDNF (Glial Cell Line-Derived Neutrotrophic factor), RET/PTC (Rearranged during transfection/Papillary Thyroid Carcinoma), GFRα (GDNF Family Receptor α), PI3K (Phosphoinositide Kinase-3), FAK(Focal adhesion kinase-1), RAS (RAt Sarcoma), AKT (serine/threonine protein kinase), MAPK (mitogen-activated protein kinase), Shc (proteins containing Src homology 2 (SH2) domains). This diagram represents the RET/PTC receptor. The RET receptor is thought to involve similar downstream pathways.

Vascular Endothelial Growth Factor Receptor (VEGFR) Pathway

The VEGFR pathway is also important in the pathogenesis of MTC.[17] Three transmembrane receptors mediate the angiogenic and lymphogenic effects of VEGF; VEGFR-1, VEGFR-2 and VEGFR-3. Of these, VEGFR-2 is believed to play the primary role in endothelial cell proliferation, migration, survival and induction of vascular permeability characteristic of neo-vascularization required for tumor growth and metastasis. VEGF proteins secreted by the tumor cell act as ligands for the VEGFR receptors and a complex feedback loop is involved in the stimulation of angiogenesis (Fig. 2).[18]

Vandetanib (ZD6474, Zactima™; AstraZeneca) (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy] quinazolin-4-amine) ZD 6474 (Zactrima, Vandetanib) is an oral anilinquinazoline compound with a molecular weight of 475 Daltons. It competes with ATP binding in the catalytic domain of several tyrosine kinases. Recombinant enzyme assays haves shown it to be a potent inhibitor of VEGFR-2 (50% inhibitory concentration [IC50] of 40 nM), with additional activity against VEGFR-3 (IC50 110 nM), EGFR (IC50 500 nM) and the rearranged during transfection (RET; IC50130 nM) kinase. Further studies on human umbilical vein endothelial cells (HUVEC) have found vandetanib to potently inhibit proliferation of VEGFR stimulated cells (IC50 60 nM) with higher doses necessary for EGFR stimulated HUVEC proliferation (IC50 170 nM). Vandetanib showed excellent selectivity for these kinases compared with related receptor tyrosine kinases, such as platelet-derived growth factor receptor (PDGFR)-β and c-Kit.[19–21] The activity profile of this agent, made it an attractive choice as a treatment for patients with unresectable MTC.

Phase I studies

Two Phase I dose escalation studies evaluating daily vandetanib alone in advanced solid tumors have been completed. The first was conducted in the United States and Australia, enrolling 77 patients, with colon cancer being the most common tumor type.[22] Dose limiting toxicities included diarrhea, hypertension and rash. The recommended dose to evaluate in further studies was 300 mg daily. This dose was tolerated well, with the most common toxicities being rash

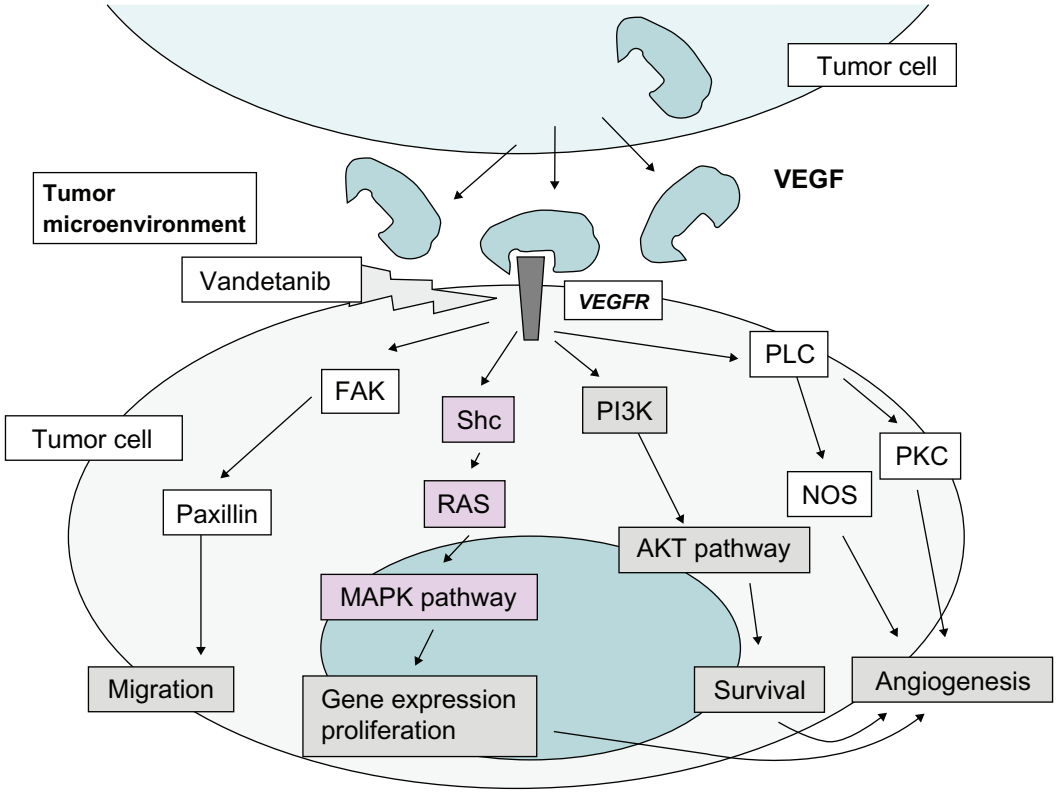

Figure 2. Interaction of tumor cells with VEGF proteins and the VEGF receptors.
VEGF (Vascular endothelial growth factor), VEGFR (Vascular endothelial growth factor receptor), FAK(Focal adhesion kinase-1), RAS (RAt Sarcoma), AKT (serine/threonine protein kinase), MAPK (mitogen-activated protein kinase) Shc (proteins containing Src homology 2 (SH2) domains), PLC (Phospholipase C), PKC (Protein Kinase C), NOS (Nitric Oxide Synthase).

and diarrhea. Asymptomatic QTc prolongation was also observed in 7 patients. Pharmacokinetic studies showed vandetanib to be extensively distributed, with a half life of approximately 120 hours 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, and enrolled 18 patients.[23] Again, 300 mg daily was determined to be the recommended dose with similar toxicity profile and pharmacokinetic findings.

Studies Involving Vandetanib and MTC (Table 1)

Single arm phase II studies

Germline mutations of RET cause the hereditary forms of MTC, one of the main targets of Vandetanib. 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. 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 7 centers. Patients received once-daily oral doses of Vandetanib 300 mg until disease progression, unacceptable toxicity, or withdrawal of consent occurred. The primary endpoint 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 the glycoprotein carcinoembryonic antigen (CEA) which are secreted by MTC cells. Between November 2004 and August 2006, a total of 30 patients were enrolled. At the time of data cutoff (February 22 2008), seventeen patients were still continuing treatment. 4 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).

Table 1. Results of studies using vandetanib in the treatment of MTC.

Study	Dose (mg)	Response rate	PFS months	Reference
08	300	20%	10.2	25
68	100	16%	Not determined	26
58	300	45	Not reached	27

The majority of patients had MEN2A and 29 of the 30 had evidence of metastatic disease at presentation. Twenty percent of subjects (6 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 to 13.2 months). The majority of patients (80%) had reductions in their calcitonin levels to less than half the baseline values for at least four weeks.[24]

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. The primary objective again was 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. 19 patients were recruited between August 2006 and May 2007 all receiving 100 mg daily initially. At the time of data cutoff 11 were continuing on this dose and the remaining 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 electrocardiogram.[25] 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.

The encouraging results of these single arm trials spurred accrual onto an international randomized phase II trial (known as the ZETA trial) comparing ZD6474 to placebo in patients with inherited and sporadic forms of MTC.[26] 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. 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 progression-free survival (PFS) with vandetanib compared to placebo. Other endpoints included evaluation of overall survival (OS) and objective response rate (ORR).

Two-year follow-up results showed that 37% of the patients had progression and 15% had died. The primary end point of the study, progression-free survival, was met with the researchers reporting a Hazard Ratio (HR) of 0.46 (95% Confidence Interval, 0.31–0.69). The median progression-free survival was 19.3 months in the placebo group and had not yet been reached in the Vandetanib arm at the time of the 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 US FDA approval, no significant OS difference was noted in the two arms because of the cross over design of the study.

Vandetanib was also associated with statistically significant advantages in secondary endpoints 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 to 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.

Based on these results, Astra Zeneca filed for Food and Drug Administration (FDA) approval of the drug in the United States and the European Medicines Agency (EMEA) in Europe late in 2010, receiving an orphan drug designation by the FDA on December 2, 2010, with final approval granted on April 6 2011.[27] 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.

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, so ECGs and levels of serum potassium, calcium, magnesium and TSH are recommended obtained at baseline, at 2–4 weeks and 8–12 weeks after starting treatment and subsequently every 3 months.

As a result of the FDA concern about toxicity, only US prescribers and pharmacies certified through the Vandetanib Risk Evaluation Mitigation Strategy (REMS) Program, a restricted distribution program, are able to prescribe and dispense vandetanib.

Future Possibilities for Vandetanib

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 further improvements in progression free and overall survival are possible and may be achieved with combination therapy using Vandetanib and either chemotherapy agents or other targeted treatments. The high cost of a new tyrosine kinase inhibitor is also likely to limit the number of patients who may have access to this medication.

Resistance may also arise in tumors exposed to Vandetanib. The authors speculate that there may be many reasons for this including new molecular abnormalities involving the 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.

Traditional Chemotherapy

Chemotherapy agents including doxorubicin and cisplatin have been evaluated in the treatment of MTC. While the medullary subgroup of thyroid cancers was thought to have the best response rates compared with differentiated and anaplastic types, no definitive studies have demonstrated a long term benefit. It has been suggested that responders to chemotherapy can see an improvement in overall survival from 5–15 months, although randomized studies proving this have been lacking.[28] Other agents such as paclitaxel and gemcitabine that have broad activity in many cancers have been disappointing with regard to their effect on MTC.[29]

The authors have seen individual patients respond to oral chemotherapy agents, as measured by biochemical and radiological criteria (unpublished data); this is consistent with published reports showing progression free intervals of 11 months to four years in patients treated with the thymidylate synthetase inhibitor capecitabine.[30] Further study should be done into newer chemotherapy agents with less toxicity and possibly in combination with targeted therapies such as Vandetanib.

Other RET and VEGFR inhibitors

Cabozantinib (XL-184)

Further investigation for a medicine with higher affinity for RET led to the development of another TKI inhibitor, XL-184 (cabozantinib), which also blocks VEGFR2 and c-MET. In a phase I trial including an expansion cohort

of 23 subjects with MTC, almost all patients showed some degree of radiographic response, with 12 (55%) out of 22 evaluable patients achieving a partial response and 84% of patients achieving stable disease lasting for more than three months. The treatment was well tolerated, with the main side effects including diarrhea, nausea, hypertension, and liver function test elevations at a dose of 175 mg daily. Long term follow up of these patients revealed a 41% partial response rate in a total of 37 patients in whom the median progression free survival had not yet been reached.[31] This promising new compound is currently being evaluated in a phase III study in which patients with unresectable locally advanced, or metastatic MTC are randomized 2:1 to receive XL-184 or placebo if they had demonstrated radiologically progressive disease prior to being enrolled.[32]

Motesanib

Motesanib (AMG-706), another multikinase inhibitor (VEGF/PDGF receptors, Kit and RET), was studied in a phase II trial of patients with advanced differentiated and medullary thyroid cancer. All patients received Motesanib 125 mg daily until disease progression or unacceptable toxicity. The results for the MTC group (n = 91) after a median follow-up of 49 weeks showed a partial response rate of 2%, according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria. However, 81% had stable disease, which lasted more than 24 weeks in 48% of patients.[33]

Axitinib

Axitinib (AG-013736) is another oral small molecule inhibitor of tyrosine kinase that effectively inhibits the VEGF receptors but not RET.[34] Nevertheless, patients with MTC were included in a multicenter, open-label phase II study looking at the use of axitinib in advanced or metastatic thyroid carcinoma. Axitinib was administered at a dose of 5 mg twice daily. Of the 60 patients who started therapy, the majority had differentiated thyroid cancer and 18% had MTC. The confirmed partial response rate was 30% by intent-to-treat analysis (31% in differentiated thyroid cancer; 18% in MTC one patient with anaplastic thyroid cancer). Responses were seen in patients despite previous treatments with a variety of chemotherapeutic regimens. Median progression-free survival was 18 months. Common adverse events included fatigue, stomatitis, proteinuria, diarrhea, hypertension and nausea.[35]

Sorafenib

Sorafenib a multikinase inhibitor targeting RET and VEGFR, was evaluated in a phase II trial in patients with advanced MTC, the primary end point of which was objective response. Secondary end points included toxicity assessment and response correlation with tumor markers, functional imaging, and RET mutations. Using a two-stage design, 16 or 25 patients were to be enrolled onto arms A (hereditary MTC) and B (sporadic MTC); all patients received sorafenib 400 mg orally twice daily. Only 5 patients were enrolled in arm A and it was therefore terminated due to slow accrual. Of 16 patients treated in arm B, one achieved a partial response (6.3%; 95% CI, 0.2% to 30.2%), 14 had stable disease (87.5%; 95% CI, 61.7% to 99.5%), and one was nonevaluable. In a post hoc analysis of 10 arm B patients with progressive disease (PD) before study, one patient had a partial response of 21 months, four patients had stable disease for 15 months, four patients had stable disease for 6 months, and one patient had clinical progression of disease. Median progression-free survival was 17.9 months. Common adverse events (AEs) included diarrhea, hand-foot-skin reaction, rash, and hypertension. Although serious adverse events were rare, one death was seen. Tumor markers decreased in the majority of patients, and RET mutations were detected in 10 of the 12 sporadic MTCs analyzed.[36]

Sunitinib

Sunitinib is a multitargeted tyrosine kinase inhibitor of VEGFR and RET making it a good candidate for a treatment of locally advanced and metastatic MTC. In a phase II study 35 patients with thyroid cancer, of whom had MTC, received 37.5 mg sunitinib daily until progression of disease or unresolved toxicities. The primary endpoint was overall response rate based on RECIST at the time of maximal response. Secondary endpoints included evaluation of time to tumor progression (TTP) overall survival (OS) and the safety and toxicity of this regimen. Three MTC patients had a partial response. The most common adverse effects were fatigue, diarrhea, hand/foot syndrome and neutropenia. Grade 3 toxicities included cytopenias (46%) diarrhea (17%), hand/foot syndrome (17%) and fatigue (11%). The median survival in this study had not been reached at the time of publication of study results.[37]

Phase III studies

To date there have been no Phase III studies using Vandetanib in MTC treatment although the randomized Phase II fulfilled the need for a comparison against a placebo arm. Further Phase III trials using this agent will likely be in the form of combination therapy compared to monotherapy, or a comparison of Vandetanib with one of the other small molecule inhibitors listed above.

Summary

Vandetanib has emerged as an effective targeted therapy in the treatment of MTC. Its recent FDA approval for patients with metastatic or unresectable disease is a landmark in the history of this condition. Its development as a targeted agent and the results of phase II and randomized studies have become a proof of principal. Future studies involving combinations with other systemic agents are eagerly awaited and may further improve upon the significant results seen to date with this agent.

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