Volume 2, Issue3, July 2011

Available Online at www.ijppronline.com

International Journal Of Pharma Professional's Research

Review Article

VANDETANIB A NEW DRUG FOR METASTATIC MEDULLARY THYROID CANCER

Sunil Kumar*, Gaurav Sharma, Mathew George, Lincy Joseph

Department of Pharmacology, Shoolini University, Solan, (H.P), India

ISSN NO:0976-6723

Abstract

Vandetanib (ZD6474; ZACTIMA™, AstraZeneca) is a once-daily, orally available agent with potential for use in a number of solid tumor types. Vandetanib targets key signaling pathways in cancer by inhibiting VEGFR-dependent tumor angiogenesis, and EGFR- and RET-dependent tumor cell proliferation and survival. Phase I studies showed vandetanib to be generally well tolerated at doses of ≤ 300 mg/day, with a pharmacokinetic profile that supports once-daily oral administration. Phase II evaluation of vandetanib in patients with advanced refractory NSCLC has demonstrated improvements in progression-free survival both as monotherapy (versus gefitinib) and in combination with docetaxel (versus docetaxel alone). These positive outcomes have led to the initiation of Phase III trials of vandetanib in advanced NSCLC. Clinical development is also ongoing in other tumor types and encouraging evidence of antitumor activity has been reported in patients with metastatic hereditary medullary thyroid cancer.

Keywords: Angiogenesis inhibitor, medullary thyroid cancer, non-small cell lung cancer, tyrosine kinase inhibitor, vandetanib, ZD6474

Introduction

The US Food and Drug Administration (FDA) has approved vandetanib (AstraZeneca) on April 7, 2011 for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. It is the first drug ever approved for the treatment of this rare form of thyroid cancer.[1] Vandetanib is the only medicine to receive FDA approval specifically for use in patients with advanced medullary thyroid cancer and is the first treatment that AstraZeneca has developed and brought to market under orphan drug designation in the United States. Vandetanib targets the ability of medullary thyroid cancer to grow and expand, according to the FDA. The use of vandetanib, a kinase inhibitor that is administered orally on a daily basis, in patients with indolent, asymptomatic, or slowly progressing medullary thyroid cancer "should be carefully considered because of the treatment-related risks," according to AstraZeneca's statement.[2] The prescribing information for vandetanib includes a box warning about treatment-related QT prolongation, Torsades de pointes, and sudden death. The study showed that for those on vandetanib, progression-free survival averaged 22.6 months, compared to 16.4 months for those on the placebo.[3] A Risk Evaluation and Mitigation Strategy (REMS) is required for vandetanib, and only prescribers and pharmacies that are certified through the vandetanib REMS program will be able to prescribe and dispense vandetanib.[2]

Correspondence Address:
Sunil Sharma
Department of Pharmacology
Shoolini university,solan (H.P)
Email:- **suny1435@gmail.com**
Mob.No:- +91-98579373

CHEMICAL STRUCTURE:

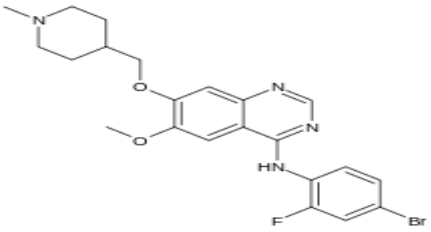

Figure 1. Chemical structure of vandetanib.[4]

IUPAC Name: *N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4yl)methoxy] quinazolin-4-amine

Vandetanib (rINN, proposed trade name Zactima), also known as ZD6474, is an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR).[5] It is a tyrosine kinase inhibitor, being developed by AstraZeneca.

MECHANISM OF ACTION:

Vandetanib is a tyrosine kinase inhibitor. Study shown (in-vitro) that vandetanib inhibit the activity of tyrosine kinases it is an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR).[1] Vascular endothelial cell growth factor receptors (VEGFR) rearrange during transfection (RET), protein tyrosine kinase 6 (BAK), TIE2, member of the EPH receptors kinase family and member of the Src family of tyrosine kinases. Vandetanib inhibit endothelial cell migration, proliferation, survival and new blood vessel formation in in-vitro models of angiogenesis. Vandetanib inhibits EGFR-dependent cell survival in vitro. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated receptor tyrosine kinase phosphorylation in tumor cells and endothelial cells and VEGF-stimulated tyrosine kinase phosphorylation in endothelial cells.

In vivo vandetanib administration reduced tumor cell induced angiogenesis, tumor vessel permeability, and inhibited tumor growth and metastasis in mouse model of cancer.[6]

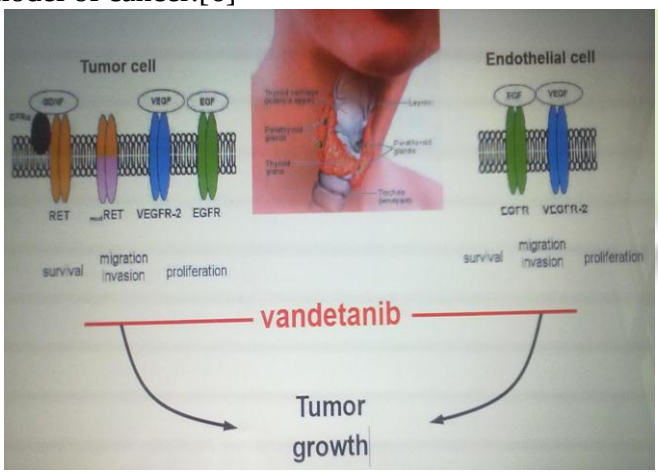

Figure 2. Mechanism of action of vandetanib[7]

RECENT ADVANCEMENT:

Vandetanib is a novel, orally available inhibitor of different intracellular signaling pathways involved in tumor growth, progression, and angiogenesis: vascular endothelial growth factor receptor-2, epidermal growth factor receptor, and REarranged during Transfection tyrosine kinase activity. Phase I clinical trials have shown that vandetanib is well tolerated as a single agent at daily doses ≤300 mg.

In the phase II setting, negative results were observed with vandetanib in small cell lung cancer, metastatic breast cancer, and multiple myeloma. In contrast, three randomized phase II studies showed that vandetanib prolonged the progression-free survival (PFS) time of patients with non-small cell lung cancer (NSCLC) as a single agent when compared with gefitinib or when added to chemotherapy. Rash, diarrhea, hypertension, fatigue, and asymptomatic QTc prolongation were the most common adverse events. Antitumor activity was also observed in medullary thyroid cancer. Four randomized phase III clinical trials in NSCLC are exploring the efficacy of vandetanib in combination with docetaxel, the Zactima in cOmbination with Docetaxel In non-small cell lung Cancer (ZODIAC) trial, or with pemetrexed, the Zactima Efficacy with Alimta in Lung cancer (ZEAL) trial, or as a single agent, the Zactima Efficacy when Studied versus Tarceva (ZEST) and the Zactima Efficacy trial for NSCLC Patients with History of EGFR-TKI chemo-Resistance (ZEPHYR) trials. Based on a press release by the sponsor of these trials, the PFS time was longer with vandetanib in the ZODIAC and ZEAL trials; the ZEST trial was negative for its primary superiority analysis, but was successful according to a preplanned noninferiority analysis of PFS. Ongoing phase II and III clinical trials will better define the appropriate schedule, the optimal setting of evaluation, and the safety of long-term use of vandetanib.[8]

EFFICACY AND TREATMENT RISK:

The approval of vandetanib is based on the results of the phase 3 ZETA study, which randomized 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer to vandetanib 300 mg (n = 231) or placebo (n = 100).

In the study, patients treated with vandetanib had a median progression-free survival of at least 22.6 months, compared with 16.4 months for patients randomized to placebo (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.24 to 0.53; $P < .0001$). "It is too early to determine the median progression-free survival in patients treated with vandetanib or to tell whether they will live longer (overall survival), compared with patients treated with placebo," according to the FDA.

Serious adverse events reported during the study resulted in 5 deaths in patients treated with vandetanib. Causes of death included breathing complications, heart failure, and sepsis. Vandetanib has been shown to affect the electrical activity of the heart, which in some cases can cause irregular heart beats that can be

life-threatening.

The prescribing information for vandetanib includes a box warning about treatment-related QT prolongation, Torsades de pointes, and sudden death.

The most common adverse drug reactions (>20%) seen in the ZETA trial with vandetanib were diarrhea (57%), rash (53%), acne (35%), nausea (33%), hypertension (33%), headache (26%), fatigue (24%), decreased appetite (21%), and abdominal pain (21%), according to the company.

A Risk Evaluation and Mitigation Strategy (REMS) is required for vandetanib, and only prescribers and pharmacies that are certified through the vandetanib REMS program will be able to prescribe and dispense vandetanib.

Vandetanib will be dispensed exclusively through the pharmacy business unit of Biologics, Inc., an integrated oncology management company, according to AstraZeneca.[9]

Vandetanib is currently under regulatory review in the European Union and Canada

COMMON SIDE EFFECT OF VANDETANIB

Vandetanib may cause serious side effects, including:

• See "What is the most important information I should know about vandetanib?"

• Serious skin reactions. Vandetanib can cause a serious skin reaction, called Stevens-Johnson syndrome or other serious skin reactions that may affect any part of your body. These serious skin reactions may be life threatening and you may need to be treated in a hospital. Call your healthcare provider right away if you experience any of these symptoms:

– Skin rash or acne
– Dry skin
– Itching
– Blisters on your skin
– Blisters or sores in your mouth
– Peeling of your skin
– Fever
– Muscle or joint aches
– Redness or swelling of your face, hands, or soles of your feet[10]

• Breathing problems (interstitial lung disease). Vandetanib may cause a breathing problem called interstitial lung disease that can lead to death. Tell your healthcare provider right away if you experience sudden or worsening shortness of breath or cough

• Stroke. Strokes have been reported in some people who have taken vandetanib and in some cases have caused death. Stop taking vandetanib and call your healthcare provider right away if you have symptoms of a stroke which may include:

– Numbness or weakness of the face, arm or leg, especially on one
side of the body
– Sudden confusion, trouble speaking or understanding
– Sudden trouble seeing in one or both eyes
– Sudden trouble walking, dizziness, loss of balance or coordination
– Sudden, severe headache

CONCLUSION: Vandetanib is a once-daily oral inhibitor of vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinases that also inhibits rearranged during transfection kinase activity. Vandetanib (300 mg/d) has previously demonstrated antitumor activity in patients with advanced hereditary medullary thyroid cancer (MTC). Vandetanib at a once-daily dose of 100 mg has clinically relevant antitumor activity in patients with locally advanced or metastatic hereditary MTC and an overall acceptable safety profile

References:

1)."FDA approves new treatment for rare form of thyroid cancer".
2).http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm250168.htm. Retrieved 7 April 2011.
3).http://www.worldpharmanews.com/astrazeneca/1636-fda-approves-orphan-drug-vandetanib
4).http://www.drugs.com/newdrugs/fda-approves-orphan-vandetanib-advanced-medullary-thyroid-cancer-2598.html
5).http://www.lookchem.com/Vandetanib/
6).http://nci.nih.gov/Templates/drugdictionary.aspx?CdrID=269177Distributed by: AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, AstraZeneca 2011 4/11 1163601 4/11
7).http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM236811.pdf
8). Morabito Allesandro et al. Vandetanib (ZD6474), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases: current status and future directions, The Oncologist Express, April 6, 2009.
9).http://www.medscape.com/viewarticle/740405
10).http://www.knowabouthealth.com/fda-approved-vandetanib-by-astrazeneca-for-medullary-thyroid-cancer/8198/