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Mini review article

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Vandetanib – a novel drug against medullary thyroid cancer

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Abstract

Despite many advances in cancer medical management, the overall survival rate of patients with cancer has not improved significantly in the past two decades. Therefore, the need for newer drugs with varied mechanism of action is the need of the hour to overcome this obstacle. The basic approach for cancer treatment is shifting from direct cytotoxic activity to other avenues. Hence, to tackle the cancerous cells, newer approaches like genetic therapies and biological response modifiers are being tried. Apoptosis is an essential physiological process in the regulation of development and maintenance of homeostasis in adult tissue; its low rate may promote survival and accumulation of abnormal cells, which leads to tumour formation. Similarly, a major characteristic of cancer cells is the loss of differentiation. Nowadays, clinical trials are carried on targeting apoptosis and cell differentiation therapy. Cancer is primarily an environmental disease, but genetics influence the risk of some cancers. An individual's hormone level is mostly determined genetically, so this may at least partly explain the presence of some cancers that run in families that do not seem to have any cancer-causing genes. One such cancer is medullary thyroid cancer, which is more likely to run in families and be associated with other endocrine problems. In fact, medullary thyroid cancer is the only thyroid cancer that can be diagnosed by genetic testing of the blood cells. A new drug called Vandetanib has been approved for the treatment of familial medullary thyroid cancer in adult patients who are ineligible for surgery. The purpose of this paper is to outline the advances in understanding the pathogenesis of medullary thyroid cancer and to summarise the results of the clinical trials of Vandetanib.

Keywords
Vandetanib; *Thyroid cancer*; *Apoptosis*; *Clinical trials*

Introduction

Abnormal kinase activity is the major cause of diseases like cancer (uncontrolled growth and division of abnormal cells) because in most cases, the kinase no longer has the ability to properly control the cellular activity. If the activity of an abnormal kinase within a cancer cell is disrupted, the cancer cell may stop growing and dividing. This type of treatment could even lead to cancer cell death, also called apoptosis. In cancer cells, cell proliferation consisting of growth and division along with other cellular pathways are constantly activated because the protein kinases that would normally control such unrestrained growth and division no longer work. The role of tyrosine kinases in cancer molecular pathogenesis is immense and recently kinases have come into vogue as potential anticancer drug targets. Vandetanib is a tyrosine kinase inhibitor, being developed by Astrazeneca. 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).[1] It has a third target, i.e. inhibiting RET-tyrosine kinase activity, an important growth driver in medullary thyroid cancer. The RET proto-oncogene encodes a receptor tyrosine kinase for members of the glial cell-line-derived neurotrophic factor family of extracellular signalling molecules.[2] A change in a gene called RET can be passed from parent to child. Nearly everyone with the changed RET gene develops medullary thyroid cancer. In April 2011, Vandetanib became the first drug to be approved by FDA for the treatment of symptomatic or late-stage (metastatic) medullary thyroid cancer in adult patients who are ineligible for surgery.[3] It is the only medicine to receive FDA approval, specifically for use in patients with advance medullary thyroid cancer.

Medullary thyroid cancer (MTC)

Medullary thyroid cancer accounts for 3–5% of the estimated 44,600 cases of thyroid cancer diagnosed each year in the United States, said the FDA in a news release. MTC is often an inherited disease in the paediatric and young adult population, resulting from gain-of-function mutations in the re-arranged during transfection (RET) proto-oncogene.[4] It begins in the C cells of thyroid. Cancer that starts in the C cells can make abnormally high levels of calcitonin. This C-cell hyperplasia is believed to be one of the initial stages during the development and progression of MTC.[5] Typical symptoms include coughing, difficulty in swallowing, thyroid enlargement, neck swelling, a lump on the thyroid and voice changes. The disease occurs alone as familial medullary thyroid cancer or with other cancers as multiple endocrine neoplasia (MEN) syndrome. A blood test can detect the changed RET gene. If it is found in a person with medullary thyroid cancer, the doctor may suggest that family members be tested. For those who have the changed gene, the doctor may recommend frequent lab tests or surgery to remove the thyroid before cancer develops. Vandetanib was evaluated in a study of 331 people with late-stage medullary thyroid cancer. Average progression-free survival among those who took the drug was 22.6 months, compared to 16.4 months among those who took an inactive Placebo, the agency said. This drug comes as a pill that is taken once

a day. In one study of patients with advanced MTC, Vandetanib stopped cancers from growing at an average of more than 6 months, when compared to Placebo (sugar pill).

Chemistry

Vandetanib is chemically described as N-(4-bromo-2-fluorophenyl0-6-methoxy-7-[(1-methyl-piperidin-4-yl)methoxy]quinazolin-4-amine). The molecular formula is $C_{22}H_{24}BrFN_4O_2$. The structural formula is:

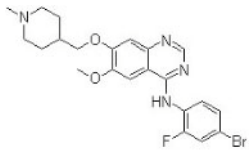

Fig. 1. Chemical structure of Vandetanib

It has a molecular weight of 475.36. It exhibits pH-dependent solubility, with increased solubility at lower pH. It is practically insoluble in water with a value of 0.08 mg/ml at 25°C (77°F).

Mechanism of action

All kinases add phosphate groups to other molecules, often other proteins, in the cell. Protein phosphorylation, the addition of a phosphate group to a side chain of an amino acid is an important regulatory action.[6] The kinases play an important role in many intracellular signalling pathways, including those that control the cell growth and cell division. Because protein kinases are activated and de-activated by the addition or removal of a phosphate, they can be inhibited by proteins that bind to the region where the phosphate normally would; thereby, block the normal activity of the protein kinase. Kinase inhibitors are a class of enzymes that regulate cellular and protein pathways by blocking the activity of protein kinases. The inhibition of such kinases may lead to death or obstructed division of cancer cells. Some of the kinase inhibitors used in treating cancer are inhibitors of tyrosine kinases.[7] Vandetanib is a kinase inhibitor. *In vitro* studies have shown that, Vandetanib inhibits the activity of kinases, including the members of epidermal growth factor receptor (EGFR) family, vascular endothelial cell growth factor receptor (VEGF), re-arranged during transfection (RET), protein tyrosine kinase 6 (BRK), TIE2, members of the EPH receptors kinase family, and the members of Src family of tyrosine kinases. It inhibits endothelial cell migration, proliferation, survival and new blood vessel formation in *in vitro* models of angiogenesis. It inhibits EGFR dependent cell survival *in vitro*. In addition, Vandetanib inhibits epidermal growth factor (EGF) stimulated receptor tyrosine kinase phosphorylation in tumour cells and endothelial cells, and VEGF-stimulated tyrosine kinase phosphorylation in endothelial cells. *In vivo*, Vandetanib administration reduced tumour cell-induced angiogenesis, tumour vessel permeability, and inhibited tumour growth and metastasis in mouse models of cancer. There is no evidence of a relationship between RET mutations and efficacy with Vandetanib.

Pharmacokinetics

A population pharmacokinetic analysis of Vandetanib was conducted in 231 patients with MTC following oral administration of 300 mg daily doses. Following oral administration of Vandetanib, administration was slow with peak plasma concentrations, typically achieved at a median of 6 h, range between 4–10 h, after dosing. It bound to human serum albumin and α-acid-glycoprotein with *in vitro* protein binding being approximately 90%. Following oral dosing of 14C-Vandetanib, unchanged Vandetanib and metabolites Vandetanib N-oxide and N-desmethyl Vandetanib were detected in plasma, urine and faeces. Within a 21-day collection period after a single dose of 14C-Vandetanib, approximately 69% was recovered with 44% in faeces and 25% in urine. Excretion of the dose was slow and further excretion beyond 21 days would be expected based on the plasma half-life.

Safety profile

It takes a long time to get rid of Vandetanib from the patient's body, and the patient may be at risk for side effects related to Vandetanib after the patient has stopped the treatment. It is not recommended to take Vandetanib, if patients have had QT prolongation. Vandetanib can cause a serious skin reaction called Stevens–Johnson syndrome or other serious skin reactions that may affect any part of the body. It may cause a breathing problem called interstitial lung disease that can lead to death. Strokes have been reported in some people who have taken Vandetanib, and in some cases it caused death. Bleeding, heart failure, diarrhoea, thyroid hormone changes, hypertension, a condition called reversible posterior leukoencephalopathy syndrome, etc. can happen as side effects while taking Vandetanib. The most common side effects of Vandetanib include: diarrhoea, rashes, acne, nausea, high blood pressure, headache, loss of appetite, tiredness and stomach pain.

Drug interactions

Drugs that are CYP3A4 inducers, e.g. Dexamethasone, Phenytoin, Rifampin, Rifabutin can alter Vandetanib plasma concentrations. The concomitant use of known strong CYP3A4 should be avoided while receiving Vandetanib treatment.

Clinical studies

A phase III, double-blind, Placebo-controlled study randomised patients with unresectable locally advanced or metastatic medullary thyroid cancer to Vandetanib 300 mg (n=231) versus Placebo (n=100) was carried by Astrazeneca.[8] Demonstration of improvement in progression-free survival (PFS) with Vandetanib compared to Placebo was the primary objective. Other end points included evaluation of overall survival and overall objective response rate (ORR). In this study, patients randomised to Vandetanib had shown a statistical significant improvement in progression-free survival (PFS) when compared to those randomised to Placebo (Hazard Ratio [HR] = 0.35; 95% Confidence Interval [CI] = 0.24–0.53; $p < 0.0001$). This difference reflected a 65% reduction in risk for disease progression. Median progression-free survival was 16.4 months in the Placebo arm and at least 22.6 months in the Vandetanib arm. At the time of primary analysis of PFS, 15% of the patients died and there was no significant difference in the overall survival between the two treatment groups. The ORR for patients randomised to Vandetanib was 44% compared to 1% for patients randomised to Placebo.[8] All objective responses were partial responses.

Conclusion

Vandetanib has shown promising clinical activity in its trial by Astrazeneca, against the treatment of progressive medullary thyroid cancer in patients with unresectable (non-operable) locally advanced or metastatic disease. Vandetanib can prolong the QT interval and cases of sudden death were reported during clinical trials. Because of this risk, Vandetanib is only available through the Vandetanib Risk Evaluation and Mitigation Strategy (REMS) programme. But

besides death cases, many patients have shown recovery, and these results have led the drug to be approved by the FDA to treat MTC that has spread. And now Astrazeneca is working to make Vandetanib available to patients as soon as possible. Vandetanib will be dispensed exclusively through the pharmacy business unit of Biologics, Inc., an integrated oncology management company.

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