Journal of Advances in Medicine and Medical Research

28(5): 1-5, 2018; Article no.JAMMR.46474
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Vandetanib and Lenvatinib for the Treatment of Thyroid Cancers

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Authors' contributions

This work was carried out in collaboration between both authors. Author HHK managed the literature searches. Author SYH wrote the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/46474
Editor(s):
(1) Dr. Syed Faisal Zaidi, Department of Basic Medical Sciences, College of Medicine, King Saud Bin Abdulaziz University-HS, National Guard Health Affairs, King Abdulaziz Medical City, Kingdom of Saudi Arabia.
Reviewers:
(1) Mohammad Nadeem Khan, Bastar University, India.
(2) Manojit Pal, Dr. Reddy's Institute of Life Sciences, Hyderabad University, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/28080

Mini-review Article

Received 11 October 2018
Accepted 30 December 2018
Published 02 January 2019

ABSTRACT

Several drugs with Rearranged during Transfection (RET) kinase-inhibitory activity were recently introduced for thyroid cancer patients. RET gene aberrations were found in differentiated thyroid cancers and medullary thyroid cancers, subsets of thyroid cancers. Rearrangement of RET gene was found in differentiated thyroid cancers and point mutations were observed in medullary thyroid cancers, and both types of RET gene change result in the ligand-independent activation of RET kinase activity. Given the relationship of RET activity and thyroid cancers, RET inhibitors were developed as anti-tumor agents for thyroid cancers. Vandetanib, sorafenib, cabozantinib, and lenvatinib was approved drugs for thyroid cancer patients, and discovery and development processes of vandetanib and lenvatinib were discussed in this review.

Keywords: RET; thyroid cancer; vandetanib; lenvatinib; kinase inhibitor; ZD6474; E7080.

1. INTRODUCTION

Recently, several RET (Rearranged during Transfection) tyrosine kinase inhibitors were introduced for thyroid cancer patients. It is encouraging news given that previously systemic chemotherapies for thyroid carcinoma patients were not available. There are vandetanib,

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cabozantinib, sorafenib, and lenvatinib approved for thyroid cancer indication.

More than 90% of thyroid cancers are the follicular or papillary cancers classified into differentiated thyroid cancer (DTC) [1]. Remaining 10% of thyroid cancers comprised of medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC). Hereditary forms of MTC is called multiple endocrine neoplasia 2A (MEN2A), MEN2B, or familial MTC [2]. Primary treatment option for thyroid cancer is surgical resection, and radioiodine therapy can be used for DTC patients. Treatment options for radioiodine-refractory DTC (RR-DTC) and unresectable advanced/metastatic MTC are limited due to the absence of effective cytotoxic chemotherapy. Discovery of RET gene aberrations were found in thyroid cancers, and this led to the RET kinase inhibitors as promising treatment options for thyroid carcinoma patients.

RET gene encodes receptor tyrosine kinase and there are two kinds of RET gene aberration resulting in constitutive activation of RET kinase activity: rearrangement and point mutations [3, 4]. Rearrangement of RET gene was found in papillary thyroid cancers. As a result of RET gene rearrangement with partner genes, fusion protein was generated containing ligand-independent tyrosine kinase activity of RET. Point mutations of RET gene conferring constitutive activation of kinase activity was observed in MTC. There are multikinase inhibitors with activity against RET kinase approved by US food and drug administration (FDA) for thyroid cancer indication – vandetanib, cabozantinib, sorafenib, and lenvatinib. In this review, discovery and development processes of vandetanib for MTC and lenvatinib for DTC were described.

2. VANDETANIB

Vandetanib (also known as Caprelsa®, ZD6474) is multi-tyrosine kinase inhibitor, suppressing the activity of multiple kinases such as RET, VEGFR (vascular endothelial growth factor receptor), and EGFR (epidermal growth factor receptor). Primary treatment for MTC is surgical resection of thyroid. For patient with metastatic MTC, treatment options were limited to radiation therapy, radiofrequency ablation, embolization, palliative resection, before the development and approval of vandetanib [2]. Vandetanib was approved for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease on 2011. Development of vandetanib made it possible for the systemic treatment of MTC.

Vandetanib is 4-anilinoquinazoline derivative (Fig. 1) and discovered as VEGFR inhibitor (Flt and KDR) [5]. Vandetanib was selected from several 4-anilinoquinazoline derivatives due to excellent solubility and good oral bioavailability. In xenograft mice model using Calu-6 lung carcinoma cell line, potent antitumor activity *in vivo* was demonstrated. Vandetanib subsequently was found to have inhibitory activity against RET kinase [6]. Chromosomal rearrangement of RET (PTC/RET) gene expressing fusion protein of RET with constitutive kinase activity was found in papillary thyroid carcinoma, and vandetanib prevented growth of cells expressing RET fusion protein *in vitro* and *in vivo* [6]. In TT and MZ-CRC-1 human MTC cell lines carrying mutation in RET mutations, cell growth was suppressed by vandetanib [7].

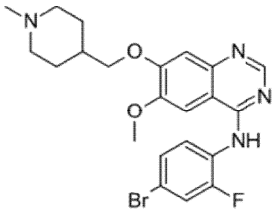

Fig. 1. Chemical structure of vandetanib

Based on these preclinical results, phase 1 clinical evaluation of vandetanib ensued, with patients of advanced solid tumors [8]. Adverse effects of vandetanib were generally mild, and common toxicities were diarrhea, hypertension, and rash. With these dose-limiting toxicities, 300 mg per day of vandetanib once daily oral administration was assessed as well-tolerated dose and utilized in phase 2 study.

Phase 2 study was carried out for patients with locally advanced or metastatic DTC [9]. The efficacy and safety of vandetanib 300 mg per day was assessed in this randomized, double-blind study. The median of progression-free survival (PFS) of patients in vandetanib treatment group was 11.1 months, while 5.9 months of median PFS were assessed in placebo group. The most common adverse effects were QTc prolongation, diarrhea, asthenia, and fatigue [9]. Another phase 2 clinical trial was performed with MTC patients [10]. With 300 mg of vandetanib treatment daily, 20% of patients exhibited partial

response and 53% of patients experienced stable disease.

Phase 3 clinical trial results with advanced MTC patients was reported [11]. The median PFS at 19.3 months in the placebo group and 30.5 months (predicted median PFS) in vandetanib treatment group. Also significant advantages of vandetanib treatment was observed in the objective response rates. Importantly, patients with M918T RET mutation showed higher response rate to vandetanib than mutation-negative patients.

With these preclinical and clinical results, vandetanib was shown to be effective treatment option for advanced or metastatic MTC. Additionally, vandetanib was demonstrated promising efficacy in dedifferentiated papillary thyroid cancer not responsive to radioiodine [12].

3. LENVATINIB

Lenvatinib (also known as Lenvima®, E7080) is also oral multi-tyrosine kinase inhibitor (Fig. 2), targeting VEGFR, fibroblast growth factor receptor, platelet-derived growth factor receptor-α (PGDFR-α), mast/stem cell growth factor receptor (SCFR, also known as kit) as well as RET proto-oncogene receptor [13]. Lenvatinib is approved by US FDA in 2015 for the treatment of progressive RR-DTC. Additionally, lenvatinib's also indicated to renal cell carcinoma and hepatocellular carcinoma patients.

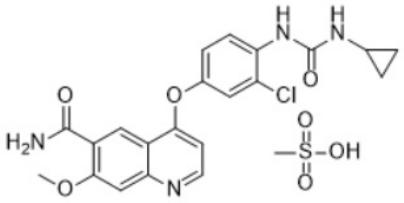

Fig. 2. Chemical structure of lenvatinib mesylate

Preclinical data showed promising antitumor activity of lenvatinib against RET gene-fusion driven tumor models and human thyroid cancer models [14,15]. Treatment of lenvatinib inhibited phosphorylation of RET in RET fusion proteins. Growth of several cell lines expressing RET fusion genes (KIF5B-RET, CCDC6-RET, NcoA4-RET) were suppressed by lenvatinib *in vitro* and *in viv*o [14]. Subsequent report by Tohyama *et al*. showed that lenvatinib effectively suppressed growth of tumor xenograft [15]. Cell lines used for xenograft implant was derived from DTC, ATC, and MTC. Lenvatinib exerted significant antitumor activity against xenografts from all thyroid cancer cell lines tested.

Phase 1 dose-escalation study was performed in patients with advanced solid tumors [16]. The maximum tolerated dose (MTD) was determined as 13 mg twice a day. Out of twenty six evaluable patients in the clinical trial, one patient exhibited partial response and stable disease was documented in 22 patients (84%). Another phase 1 trial with advanced, refractory solid tumor patients, MTD was determined as 25 mg per day similar to prior trial [17]. 9% of partial response and 46% of stable disease for the clinical test indicated encouraging anti-tumor efficacy of lenvatinib.

Phase 2 clinical results were obtained from patients with advanced RR-DTC patients [18]. Fifty-eight patients were given oral administration of lenvatinib 24 mg once daily until disease progression. Partial response rate was 50% and no complete response was reported. A time to response was 3.6 months and a median PFS was 12.6 months, supporting further clinical study of lenvatinib.

Phase 3 clinical test for lenvatinib is called SELECT (Study of E7080 LEvantinib in differentiated Cancer of the Thyroid), randomized, double-blind, multicenter study with progressive RR-DTC patients [19]. Patients were randomly assigned to 24 mg per day of lenvatinib group and placebo group. The median PFS was 18.3 months in the lenvatinib group and 3.6 months in the placebo group. The overall response rate was 64.8 % in the lenvatinib group and 1.5% in the placebo group. Adverse events were hypertension, diarrhea, fatigue or asthenia, decrease appetite, weight loss, and nausea. Based on this SELECT trial showing significant improvement of lenvatinib efficacy, lenvatinib is currently indicated for RR-DTC patients.

4. CONCLUSION

Since the discovery of RET proto-oncogene involvement in thyroid carcinoma development, small molecule inhibitors of RET tyrosine kinase activity was explored for the clinical benefit. The application of RET inhibitors such as vandetanib and lenvatinib to thyroid carcinoma was successful, thus provided novel treatment option as systemic therapy for DTC and MTC patients. Adverse events of vandetanib or lenvatinib

treatment were considerable, thus management of toxic effects and optimization of treatment scheme will be required.

Alteration of RET gene was observed in neoplasms other than thyroid carcinomas. For example, KIF5B (kinesin family 5B)-RET and CCDC6 (coiled coil domain containing 6)-RET fusion in non-small cell lung cancer, BCR (breakpoint cluster region)-RET and FGFR10OP (fibroblast growth factor receptor 10 oncogenic partner)-RET fusion in leukemia were observed [20]. Recent results from primary ATC cells indicate that potential efficacy of vandetanib and lenvatinib against ATC [21]. Thus, RET inhibitor's indication is expected to extend to other types of malignancies in the future.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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