Review

Lenvatinib: A Promising Molecular Targeted Agent for Multiple Cancers

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Abstract

Lenvatinib is a small-molecule tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR1-3), fibroblast growth factor receptor (FGFR1-4), platelet-derived growth factor receptor α (PDGFRα), stem cell factor receptor (KIT), and rearranged during transfection (RET). These receptors are important for tumor angiogenesis, and lenvatinib inhibits tumor angiogenesis by inhibiting function of these receptors. Phase I trials of lenvatinib were conducted at the same time in Japan, Europe, and the United States, and tumor shrinkage effects were observed in thyroid cancer, endometrial cancer, melanoma, renal cell carcinoma, sarcoma, and colon cancer. Lenvatinib is a promising drug that has shown therapeutic effects against various solid tumors. Adverse events, such as hypertension, proteinuria, diarrhea, and delayed wound healing, can occur with lenvatinib treatment. Managing these adverse events is also important for the use of lenvatinib. In this mini-review article, we outline the current state, toxicity, and future prospects of lenvatinib toward thyroid cancer, hepatocellular carcinoma, renal cell carcinoma, and lung cancer.

Keywords

targeted therapy, lenvatinib, hypertension, thyroid cancer, KIT

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Introduction

Since the clinical application of rituximab for cancer in the early 1990s, molecular-targeted agents continue to be developed as mainstream anticancer drugs. Molecular-targeted agents are generally classified based on their structure into antibody and small-molecule compounds. Antibody compounds bind to specific receptors present on the surface of cell membranes, thereby inhibiting downstream signaling related to cell proliferation. Small-molecule compounds pass through the cell membrane and most of them function as tyrosine kinase inhibitors and directly inhibit nuclear signal transduction. Each compound targets molecules that are overexpressed in various malignant tumors, which is the reason these compounds are called "molecular-targeted drugs." These drugs were originally considered to have few adverse effects because they target malignant cells. However, after introduction into clinical practice, many adverse cytotoxic effects have been observed. More than 50 kinds of molecular-targeted drugs are currently used in clinical practice.

Lenvatinib is a tyrosine kinase inhibitor that is being developed as a molecular-targeted drug. In this mini-review article, we outline the current state, toxicity, and future prospects of lenvatinib.

What Is Lenvatinib?

Lenvatinib was identified through the exploratory research of agents with various tyrosine kinase inhibitory activities related to angiogenesis.[1-4] Lenvatinib is a small-molecule tyrosine

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kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR1-3), fibroblast growth factor receptor (FGFR1-4), platelet-derived growth factor receptor α (PDGFRα), stem cell factor receptor (KIT), and rearranged during transfection (RET). These receptors are important for tumor angiogenesis, and lenvatinib inhibits tumor angiogenesis by inhibiting function of these receptors. Moreover, FGFR, RET, PDGFRα, and KIT are involved in the proliferation of cancer cells, and thus, lenvatinib is expected to directly inhibit cancer cell proliferation through blocking the signal transduction pathways involving these factors.

Phase I trials of lenvatinib were conducted at the same time in Japan, Europe, and the United States,[5-10] and tumor shrinkage effects were observed in thyroid cancer, endometrial cancer, melanoma, renal cell carcinoma (RCC), sarcoma, and colon cancer. The maximum tolerated dose from these trials was 25 mg. The main toxicities of lenvatinib were high blood pressure, proteinuria, and fatigue. After these trials, the recommended dose of lenvatinib was established as 24 mg once daily.

Lenvatinib and Thyroid Cancer

Based on the results of phase I studies of lenvatinib to radioactive iodine refractory differentiated thyroid cancer (RIR-DTC), lenvatinib had been developed toward RIR-DTC. Two phase II trials of lenvatinib were conducted in Europe and the United States. In one study, lenvatinib (starting dose, 24 mg daily) was administered to 58 patients with RIR-DTC (43 papillary carcinomas, 15 follicular carcinomas). The response rate (RR) as the primary end point was 50% (95% confidence interval [CI]: 37%-63%), and the median progression-free survival (PFS) was 12.6 months.[11] In another study, 59 patients with advanced medullary thyroid carcinoma were treated by lenvatinib (starting dose also 24 mg daily). The RR was 36% (95% CI: 24%-49%), the disease control rate (DCR) was 80%, and median PFS was 9.0 months.[11] Based on these promising results, the phase III study of (E7080) lenvatinib in differentiated cancer of the thyroid (SELECT) trial was conducted. In this trial, 392 patients with RIR-DTC from 21 countries were enrolled and randomly assigned to the lenvatinib group and the placebo group at a ratio of 2:1.[12] The median PFS (primary end point) was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio [HR] = 0.21, $P < .001$). However, there was no significant difference in the overall survival (OS) between the 2 groups. The lack of this significance might be due to permitting crossover to the lenvatinib after disease progression in the placebo group. The RR was 64.8% in the lenvatinib group and 1.5% in the placebo group. An incidence rate of grade 3 or higher adverse event in the lenvatinib group was as high as 75.9% and mostly hypertension and proteinuria (Table 1).[12] To adjust for crossover and to estimate the true OS treatment effect (the effect that would have been observed in the absence of switching), a rank preserving structural failure time (RPSFT) model was used in another analysis for this trial.[13] With the RPSFT adjustment, HR was 0.62 (95% CI: 0.40-1.00), indicating a trend for longer survival for the lenvatinib arm versus the placebo crossover arm ($P = .0510$). Newly published data confirmed that lenvatinib in comparison to placebo prolongs OS even in patients after 65 years of age.[14]

Table 1. Incidence rate of ≥grade 3 adverse event of the lenvatinib (SELECT trial[12]).

	Lenvatinib (n = 261)		Placebo (n = 131)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any adverse effect, %	97.3	75.9	59.5	9.9
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8.0	8.4	0
Fatigue or asthenia	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Nausea	41	2.3	13.7	0.8
Palmar-plantar erythrodysesthesia syndrome	31.8	3.4	0.8	0
Proteinuria	31.0	10.0	1.5	0

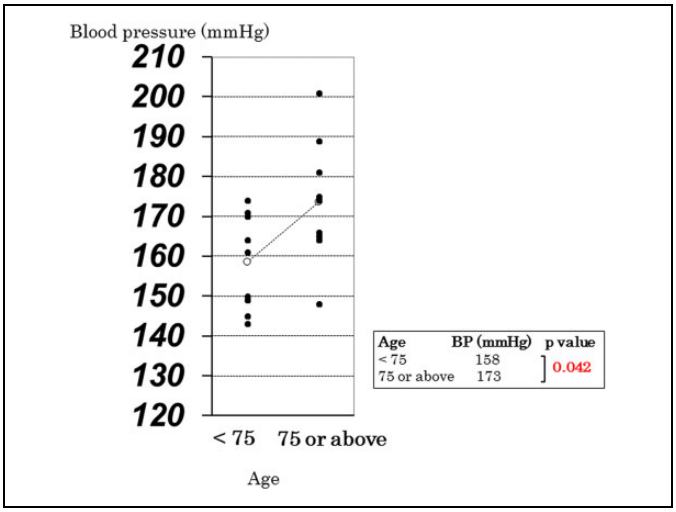

Figure 1. Effects of lenvatinib on hypertension between differentiated patients with thyroid cancer <75 and ≥75 years old. Patients ≥75 years old showed significantly higher systolic blood pressure than patients <75 years old.[15]

Based on these trials, lenvatinib has been approved in the United States, Japan, and other countries for RIR-DTC and is used in clinical practice. However, patients administered lenvatinib are reported of bleeding from tumor involving skin and large vessels by the fistula formation. The same response was observed in our institution.[15] Although a retrospective analysis from a single institution, there was a report of an increased frequency of hypertension, which is a typical adverse event of lenvatinib, especially in elderly patients aged 75 years or older (Figure 1).[15] In clinical practice, the number of cases using lenvatinib will increase, and thus, these adverse events caused by lenvatinib should be monitored.

A small analysis of lenvatinib efficacy to anaplastic thyroid cancer (ATC) was performed in Japan.[16] In this study, lenvatinib was administered to 17 patients with ATC. The RR was

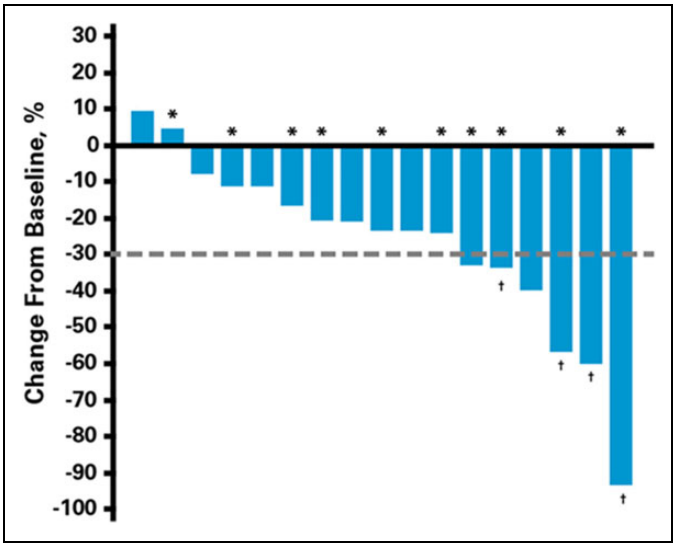

Figure 2. Effects of lenvatinib for ATC. Lenvatinib exhibited tumor shrinkage effects in almost all patients with ATC. ATC indicates anaplastic thyroid cancer.[16] *indicates Anaplastic thyroid cancer confirmed by independent pathologic review; †patients with partial response as best overall response.

24%, DCR was 94%, median PFS was 7.4 months, and median OS was 10.6 months. These results are relatively good for ATC. Some patients accomplished long therapeutic effect of lenvatinib (Figure 2).[16] Based on this result, lenvatinib has been approved for ATC in Japan. There have been some cases of administering lenvatinib for ATC in our institution. Each patient showed good response or disease control. But another retrospective study from Mayo clinic observed benefits of lenvatinib for ATC were transient and toxicities were prominent.[17]

Lenvatinib and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) cases typically express high levels of VEGF. Sorafenib, a tyrosine kinase inhibitor that blocks the VEGF signal transduction pathway, is the first anticancer agent for metastatic HCC. A previous study showed that treatment of HCC by sorafenib improved OS.[18] However, because of its strong toxicity including hand–foot syndrome and its limited efficacy toward OS (almost 1 year), new drugs have been pursued. From the phase I trial for HCC with Child-Pugh A, a recommended dose of lenvatinib of 12 mg for HCC was determined.[19] This dose is half of that for thyroid cancer. A subsequent phase II trial of lenvatinib (starting dose 12 mg/d) for HCC evaluated 46 patients and found that median time to progression was 7.4 months, median OS was 18.7 months, RR was 37%, and DCR was 78%.[20] These results were notable for metastatic HCC. Based on this result, the phase III trial was conducted, comparing the efficacy of lenvatinib and sorafenib toward systemic chemotherapy-naive patients with metastatic HCC.[21] The trial results demonstrated noninferior efficacy of lenvatinib to sorafenib in OS (primary end point). Progression-free survival, time to treatment failure, and RR (secondary end points) were better significant in the lenvatinib group.

Lenvatinib and RCC

Clear cell carcinoma accounts for 70% to 80% of RCC and occurs frequently in Von Hippel-Lindau (VHL) disease. The VHL gene product is an essential molecule for ubiquitination that is necessary for the degradation of hypoxia-inducing factor 1α. In addition, VEGF is one of the target genes of the VHL protein. Aberrant expression or function of VHL gene can lead to overexpression of VEGF, and this overexpression of VEGF is considered to be involved in the development of RCC. Therefore, in RCC, the development of molecular-targeted agents targeting the VEGF pathway is increasing. Sorafenib, sunitinib, pazopanib, and axitinib are currently administered for treatment of RCC. In addition, everolimus and temsirolimus, which target mammalian target of rapamycin (mTOR) located downstream of the VEGF pathway, have also been shown to be effective.

Lenvatinib, a tyrosine kinase inhibitor that inhibits VEGFR1-3, is also expected to have effects on RCC. A randomized phase II trial was conducted comparing the effects of lenvatinib monotherapy (24 mg), lenvatinib (18 mg) combined with everolimus (5 mg), and everolimus monotherapy (5 mg) for patients with RCC who were pretreated with antiangiogenic inhibitors. Progression-free survival, the primary end point, was significantly prolonged in the combination group (14.6 months) compared with the everolimus group (5.5 months). The PFS of the combination group was also prolonged compared with that of lenvatinib monotherapy group (7.4 months). The median OS was 25.5 months in the combination group, 15.4 months in the everolimus group, and 18.4 months in the lenvatinib group, but there were no significant differences among these results.[18] Based on these results, the US Food and Drug Administration (FDA) approved lenvatinib and everolimus therapy for RCC pretreated with antiangiogenic inhibitors.

A phase III trial is currently ongoing to analyze the effect of lenvatinib plus everolimus therapy or lenvatinib plus pembrolizumab therapy compared with standard sunitinib monotherapy in the first-line setting in RCC.

Lenvatinib and Lung Cancer

Lenvatinib is also under development for treatment in lung cancer. A randomized phase II trial of the patients with nonsquamous, non-small cell lung cancer after third-line chemotherapy was reported in the 2014 Annual Meeting of American Society of Clinical Oncology.[22] Median OS (primary end point) was 38.4 weeks in the lenvatinib group compared to 24.1 weeks in the placebo group. Although there was no significant difference between these 2 groups (HR: 0.7, $P = .065$), there was tendency of longer OS in the lenvatinib group. The single-arm phase II trial was reported in the 2016 Annual Meeting of European Society of Medical Oncology; the trial verified the efficacy of lenvatinib for patients of RET-positive lung adenocarcinoma. Rearranged during transfection gene–positive patients account for 1% to 2% of all lung adenocarcinoma patients. Good results were reported from this trial; the DCR

was 76% and median PFS was 7.3 months.[23] However, a phase III trial of lenvatinib for lung cancer has not yet been conducted.

Lenvatinib and Combination Therapy With Immunocheckpoint Inhibitors

The development of combination therapy of lenvatinib and an anti-PD-1 antibody pembrolizumab has been started for various solid tumors. From the ongoing phase Ib/II trials, a high RR of less than 70% has been reported. However, combination therapy with molecular-targeted agents or cytotoxic drugs and immunocheckpoint inhibitors may cause unexpected adverse events, and careful development is required.

Toxicity of Lenvatinib

Many adverse effects of lenvatinib have been reported, including hypertension, hand–foot syndrome, diarrhea, and thrombocytopenia. Zhu et al analyzed the safety and efficacy profiles of lenvatinib in patients with cancer in a systematic review and meta-analysis.[24] In this analysis of lenvatinib-treated patients, the most frequently observed adverse events of grade 3 or higher were thrombocytopenia (25.4%), hypertension (17.7%), and peripheral edema (15.5%). In the phase III SELECT trial of thyroid cancer, the most common reasons for dose reduction were diarrhea, hypertension, and proteinuria.[12] In fact, most patients in our daily clinical practice cannot continue lenvatinib at the starting dose of 24 mg.

In addition, nephrotic syndrome, delayed wound healing, and cardiac dysfunction are also adverse effects of lenvatinib which must be carefully monitored. Lenvatinib must be used with careful monitoring of these adverse events and continued until its side effects are well controlled.

Conclusions

Lenvatinib is a promising drug that has shown therapeutic effects against various solid tumors. Adverse events, such as hypertension, proteinuria, diarrhea, and delayed wound healing, can occur with lenvatinib treatment. Furthermore, combined use with immunocheckpoint inhibitors also suggests the possibility of further adverse events. Through appropriate management of lenvatinib in clinical practice, maximum clinical effects must be obtained for thyroid cancer. At the same time, appropriate development must be accomplished for the usefulness of lenvatinib toward many types of cancers.

Declaration of Conflicting Interests

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