

ARTICLE

Pharmacodynamic analysis of hypertension caused by lenvatinib using real-world postmarketing surveillance data

Yuki Otani | Hidefumi Kasai | Yusuke Tanigawara

Department of Clinical Pharmacokinetics and Pharmacodynamics, Keio University School of Medicine, Tokyo, Japan

Correspondence

Yusuke Tanigawara, Department of Clinical Pharmacokinetics and Pharmacodynamics; Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, Tokyo 160-8582, Japan.
Email: tanigawara-yusuke@umin.ac.jp

Abstract

Lenvatinib is a tyrosine kinase inhibitor of the vascular endothelial growth factor receptor used against nonoperative thyroid cancer; however, hypertension is a major dose-limiting side effect. In this study, hypertension caused by lenvatinib was described through a novel population pharmacodynamic model using postmarketing surveillance data obtained in Japan. The model consists of two maximum effect model components based on the (1) concentration of lenvatinib in plasma and (2) cumulative area under the curve of lenvatinib. In addition, antihypertensive drug of either an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or calcium channel blocker accounted for by lowering effect on diastolic blood pressure. Based on virtual simulations, the combination of antihypertensive drug and dose adjustment of lenvatinib showed a reduction in the probability of grade greater than or equal to 3 hypertension. The present model provides useful guidance in managing hypertension during treatment with lenvatinib in the real-world setting.

INTRODUCTION

Physiologically, vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) play a critical role in vascular development, angiogenesis, and neogenesis, which contribute to the growth and spread of tumors.¹ The development of VEGFR inhibitors is a valuable strategy in the management of malignancies.

Lenvatinib is an oral, multitargeted, tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, fibroblast growth factor receptor 1 (FGFR1), FGFR2, FGFR3, FGFR4, RET proto-oncogene, stem cell factor receptor (KIT), and platelet-derived growth factor receptor α .^{2,3} Lenvatinib was launched in Japan in 2015 for the treatment of nonoperative thyroid cancer. It demonstrated prolonged median progression-free survival (lenvatinib: 18.3 months; placebo: 3.6 months; hazard ratio: 0.21; $p < 0.001$) and improved overall response

rate (64.4% vs. 1.5%, respectively; $p < 0.001$) compared with placebo in the pivotal Phase III study of lenvatinib in radioiodine-refractory differentiated thyroid cancer (SELECT) trial.⁴

Hypertension (HTN) is a serious dose-limiting side effect of lenvatinib that targets the VEGF pathway.⁵ In most patients, HTN is manageable by supportive therapy (e.g., antihypertensive treatment). However, in a subgroup analysis of the SELECT trial, there was a higher incidence of HTN in the Japanese population (any grade: Japanese, 87%; overall, 68%; grade ≥ 3 : Japanese, 80%; overall, 42%) and more frequent dose reductions (Japanese, 90%; overall, 67.8%) due to adverse events.⁶ This result implies that a significant number of Japanese patients using lenvatinib in the real-world setting may experience HTN during treatment, thereby potentially limiting treatment efficacy due to dose reduction. Therefore, it is essential to obtain more detailed information regarding

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the safety and toxicity of treatment with lenvatinib, especially in the Japanese patient population with higher incidence rates.

Population pharmacokinetic/pharmacodynamic (PopPK/PD) modeling for the adverse effects of anticancer drug treatment is widely used in the oncology field. Hansson et al.⁷ and Chen et al.⁸ applied a linear exposure-response model for sunitinib and axitinib, respectively, to describe continuous measurements of adverse events, such as HTN. Keizer et al.^{9,10} developed a PopPK/PD model for HTN following treatment with lenvatinib using Phase I study data from 67 patients. In an analysis of the antitumor effect and safety profile of lenvatinib, Hayato et al.¹¹ reported that once-daily 18 mg dose without uptitration was more appropriate than the approved once-daily 24 mg dose. However, to the best of our knowledge, there are no studies describing a PopPK/PD model of lenvatinib-induced HTN using large-scale, real-world data.

Japanese regulations require mandatory postmarketing surveillance (PMS) of new chemical entities and biological products to confirm their safety. Various safety and toxicity profiles, including HTN, have been reported by physicians who prescribe lenvatinib. Classical PMS analysis collected the safety data (e.g., high blood pressure [BP] events, liver dysfunction, etc.) from the sample population and simply calculated frequencies for a variety of adverse events. Risk factors were searched for any empirical associations with patient demographic factors in a retrospective manner. Thus, the traditional analysis is limited to a “description” of the data. To overcome this limitation of the classical analysis, we have utilized these observational safety data to develop a PopPK/PD model for describing the relationship between exposure to lenvatinib and occurrence of HTN in a large patient population in a real-world clinical setting. This study aimed to describe the exposure-response models for the time course of diastolic BP (dBp) and to simulate the lenvatinib-induced HTN in different baseline dBp and dosing regimen settings, illustrating the effect of antihypertensive treatment and lenvatinib dose reduction for the treatment of elevated dBp.

MATERIALS AND METHODS

Patients

All lenvatinib-naïve inoperative patients with thyroid cancer in Japan who were treated with lenvatinib between May 2015 (drug launch on the market) and November 2015 were included in the study (584 patients). The demographics, medication use (including antihypertensive treatment), and safety data were obtained through PMS. Data collection was performed at baseline prior to treatment and several times during treatment or at discontinuation of lenvatinib using case report forms from the participating sites.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Lenvatinib increases blood pressure (BP), leading to dose-limiting toxicity, especially in the Japanese population. However, use of a high-dose regimen is considered crucial in antitumor treatment. Population pharmacokinetic/pharmacodynamic (PK/PD) modeling was applied to describe the adverse effect using data obtained from premarketing clinical trials.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can a PK/PD model of lenvatinib-induced hypertension be described using real-world postmarketing surveillance data?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Diastolic BP increases with increasing lenvatinib exposure described by the direct response maximum effect model, with reduction in diastolic BP by concurrent antihypertensive treatment. Simulations using the developed PK/PD model showed reduction in the probability of developing grade greater than or equal to 3 hypertension during antihypertensive treatment with the stepwise reduction of lenvatinib dose.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The present results provide useful guidance for treatment with lenvatinib and management of hypertension. This study also provides a successful example utilizing real-world surveillance data for model-informed dose optimization.

The PMS was conducted in accordance with the Declaration of Helsinki and the Good PostMarketing Study Practice ordinance in Japan. This study used only unlinkable anonymized data in accordance with the privacy protection law in Japan. The Ethics Committee of Keio University School of Medicine (Tokyo, Japan) approved the retrospective PD analysis of lenvatinib using anonymous data collected through the PMS method (Authorization number: 20180148).

Data collection

PMS data for treatment with lenvatinib included baseline characteristics, such as age, gender, body weight, Eastern

Cooperative Oncology Group Performance Status, tumor histology (i.e., differentiated, medullary, and anaplastic), study period, baseline systolic BP (sBP), baseline dBP, comorbidities, baseline antihypertensive treatment (i.e., diuretics, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [ACEi/ARB], calcium channel blocker [CCB]), and baseline levothyroxine treatment), lenvatinib dosing conditions, complete blood counts (especially hemoglobin level), and serum chemistry data (serum albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine). Collection of all laboratory parameters was arbitrary with respect to time because examination and treatment schedules varied according to the clinical circumstances of patients.

Primary outcome events for safety analysis included change in sBP and dBP over time. The observational period for sBP, dBP, timing of antihypertensive treatment, and dose reduction of lenvatinib also varied among patients.

PopPK/PD model for lenvatinib

The concentrations of lenvatinib in plasma were simulated using a PopPK model developed by Gupta et al.¹² utilizing pooled data from 15 Phase I–III clinical trials that enrolled both healthy volunteers and patients with solid tumors, thyroid cancer, or radioiodine-refractory differentiated thyroid cancer. Gupta et al.¹² reported that lenvatinib PK be described by a three-compartment model with linear elimination from the central compartment. They analyzed 590 patient data, in which 91 patients (11.7%) were Japanese. They also reported that there was no significant difference in PK in different ethnicity. Clearance depended on the values of albumin, alkaline phosphatase, and use of CYP3A4 inducer and inhibitor. Body weight was related to the values of Q_2 , Q_3 , intercompartmental clearance between central and two peripheral compartments, and volume of distribution for each compartment (i.e., V , V_2 , and V_3). Interindividual variabilities for the PK parameters reported by Gupta et al.¹² were utilized in the present PopPK/PD analysis.¹³

The Framingham Heart Study demonstrated that systolic HTN is more important as a predictor of cardiovascular outcomes.¹⁴ Hence, the focus of research has been on systolic HTN. However, a recent prospective cohort study consisting of 93,303 individuals showed the impact of dBP on the risk of developing HTN compared with optimal BP was significantly greater than that of sBP.¹⁵ In an analysis using data from 1.3 million adults in the general outpatient population, it was revealed that elevations in sBP and dBP independently influenced the risk of adverse cardiovascular events.¹⁶ Therefore, there is a strong interest in dBP-related HTN. Previous similar studies evaluating the relationship

between VEGFR-mediated increase in BP and exposure or efficacy end points relied on dBP values, as measurements of sBP are associated with higher lability.^{8,17,18} Thus, in the current PopPK/PD analysis, we decided to perform the assessment using dBP values.

Regarding the PD modeling of dBP, we have investigated a combination of three structural models considering calculated concentration (C ; i.e., linear, log-linear, and maximum effect [E_{max}]) with three different response models (i.e., direct, indirect, and effect compartment). Model selection was guided by plausible parameter estimates, precision of the parameters, visual diagnostics, and mainly by the minimum objective function value (OFV) computed using the Phoenix NLME software version 8.1 (Certara, Princeton, NJ). The OFV was provided as proportional to twice the log-likelihood. Reduction in OFV of greater than or equal to 3.84 was considered a significant improvement ($p < 0.05$) in model description.

Mainly three types of antihypertensive therapy were used as supportive care: ACEi/ARB, CCB, and diuretics. However, because the use of diuretics was very infrequent (<10% of total), the effect of this category of agents was not considered in the model. Three patterns of the effect of antihypertensive therapy were considered, and each was expressed as a categorical variable (0/1); “ACEi/ARB use” (model A), “CCB use” (model C), and “either ACEi/ARB or CCB use” (model AC). Models A, C, and AC all presented a direct negative effect on dBP. The concurrent use of antihypertensive therapy was appropriately modified during the course of lenvatinib treatment in individual patients, and therefore the above covariates indicating use of the antihypertensive treatment varied over time within individuals.

Determination of clinical factors that affect safety

Clinical factors were screened as potential covariates that could affect the change in dBP using a stepwise covariate modeling approach with forward selection ($p < 0.05$) and backward elimination ($p < 0.01$). The potential factors analyzed as covariates included demographics (i.e., age, gender, Eastern Cooperative Oncology Group Performance Status, and histology), baseline dBP, and laboratory data (hemoglobin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine). All potential factors were included to test with all PD structural parameters. The continuous covariates were modeled as a power function and centered at the reference value (Ref_{cov}) using covariate scale factor θ_{cov} as shown:

$$\theta = \theta_{tv} \times \left(\frac{\text{Covariate}}{Ref_{cov}} \right)^{\theta_{cov}}$$

Final covariate selection was performed using the likelihood ratio test based on differences in the OFV.

Model evaluation

Goodness-of-fit plots and visual predictive checks were used to evaluate the model. The final model was simulated 1000 times and 95% confidence intervals (CIs), as well as the 5th, 50th, and 95th percentiles of the simulated data were compared with the corresponding percentiles of the observed data. The model was considered adequate if the observed data were distributed within the 5th and 95th percentiles of the simulated data.

The stability and performance of the final PK/PD model was also investigated through a nonparametric bootstrap analysis. The final model was refitted to each of the randomly sampled replicate of the original data (i.e., one at a time), and this process was repeated 200 times with different random draws. The mean, SE, and 95% CIs for the population parameters were obtained.

Dosing regimen simulations

Lenvatinib is available as a 4 or 10 mg hypromellose hard capsule formulation. Therefore, lenvatinib-induced HTN was simulated for 14, 20, and 24 mg dose without uptitration in a dBP baseline of 60 and 90 mmHg accordingly. Using simulated dosing histories, the exposure-response model was applied to predict the time course of dBP change over 16 weeks. The scenarios included introduction of an antihypertensive drug on week 2, and dose reduction was performed on weeks 6 and 12 to simulate the effect of antihypertensive treatment and dose reduction of lenvatinib. Each scenario of the lenvatinib dosing regimen was simulated 1000 times using the final PK/PD model to estimate the 25th, 50th, and 75th percentiles of the simulated dBP, and compared with treatment-emergent HTN (TE-HTN).

HTN was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We have defined TE-HTN as grade 3 HTN (equivalent to stage 2 HTN: sBP \geq 160 mmHg or dBP \geq 100 mmHg) for which medical intervention is indicated.¹⁹ All comparisons between dosing regimens based on model simulations were descriptive.

Software

Exposure-response analysis for change in dBP and simulations were performed using the Phoenix NLME software version 8.1 (Certara) with an HP Z640 workstation (Intel

Xeon E5 processor, 2.60 GHz, 28 cores). The FOCE ELS computational algorithm was used. The post hoc analysis of antihypertensive effect was calculated using Monolix (Lixoft). The model codes for Phoenix NLME and Monolix are provided in Text S1 and S2, respectively.

Ethical approval

The PMS of lenvatinib was performed in accordance with the Japanese regulatory requirements termed “Good Post-Marketing Study Practice (GPSP).” All personal information related to the surveillance was managed anonymously in accordance with the “Act on the Protection of Personal Information.” The Ethics Committee of Keio University School of Medicine (Tokyo, Japan) approved the retrospective PD analysis using anonymous data collected by the PMS surveillance of lenvatinib (2018-0148).

RESULTS

Study population and patient characteristics

Patients enrolled in this study received treatment with lenvatinib for unresectable thyroid cancer for the first time, and underwent measurements of BP. A flowchart showing the selection of the final study population is presented in Figure 1. Of the 584 patients, 104 patients were excluded due to lack of data regarding gender (2 patients), body weight (32 patients), dosing regimen (7 patients), and BP (60 patients). In total, 480 patients with a total of 6388 BP measurements were eligible for the PD analysis.

Characteristics of the study population are shown in Table 1. The median age of patients was 70 years (interquartile range: 63–77 years), and 41.8% were men. Median BP at baseline was 125/73 mmHg, and most patients were receiving thyroxine for hormone replacement. The treatment schedule was modified, doses were skipped, or treatment was discontinued mainly based on the severity of adverse events in accordance with the CTCAE version 4.0. However, the final decision regarding the dosing regimen was at the physician’s discretion. Examples of observed data trend (dBP measurement, lenvatinib dosage, and the use of antihypertensive treatment) are shown in Figure S1.

PK/PD model development

Out of all structural models tested, a direct response E_{\max} model was most appropriate to describe the observed data. Through model building process, we found that the dBP changes were not only related to concentrations of lenvatinib

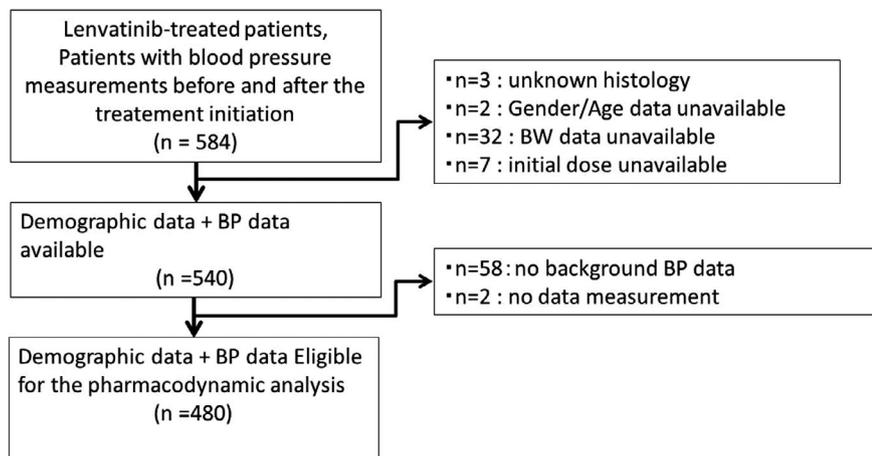


FIGURE 1 Overview of the study population of lenvatinib-treated patients with unresectable thyroid cancer. Of the initial patient population ($n = 584$), a total of 480 patients were eligible for pharmacodynamic analysis. BP, blood pressure; BW, body weight

TABLE 1 Demographics and baseline characteristics of lenvatinib-treated patients with thyroid cancer

	Total ($n = 480$)	Differentiated ($n = 356$)	Medullary ($n = 20$)	Anaplastic ($n = 104$)
Median age, years (IQR)	70 (63.0–77.0)	70 (63.0–77.0)	63 (49.8–67.5)	72 (64.3–78.0)
Male, n (%)	200 (41.7)	144 (40.4)	14 (70.0)	42 (40.4)
Median weight, kg (IQR)	60 (53.6–68.4)	62.3 (54.0–68.9)	58 (48.0–74.4)	56.3 (53.3–61.7)
Female, n (%)	280 (58.3)	212 (59.6)	6 (30.0)	62 (59.6)
Median weight, kg (IQR)	47.3 (42.1–54.0)	48.5 (43.6–55.8)	52.0 (40.2–66.7)	47.0 (40.0–52.1)
ECOG PS, n (%)				
0–1	407 (84.8)	313 (87.9)	19 (95.0)	75 (72.1)
2	40 (8.3)	25 (7.0)	1 (5.0)	14 (13.5)
≥ 3	33 (6.9)	18 (5.1)	0 (0.0)	15 (14.4)
Histology, n (%)				
Papillary		262 (73.6)		
Follicular		46 (12.9)		
Poorly differentiated		42 (11.8)		
Others/multiple origin		9 (2.5)		
Median time of study, days (IQR)	146 (74.0–288.0)	181 (91.0–361.0)	251.5 (120.0–361.0)	69 (25.3–157.0)
Median sBP at baseline, mmHg (IQR)	125 (112.0–134.0)	126 (115.0–135.0)	122 (104.3–129.8)	122 (110.3–132.0)
Median dBP at baseline, mmHg (IQR)	73 (64.0, 81.0)	73 (65.0, 81.0)	71 (60.3, 80.8)	71 (63.3, 80.0)
Patients using thyroid medication at baseline, n (%)	430 (89.6)	339 (95.2)	19 (95.0)	72 (69.2)
Patients using diuretics at baseline, n (%)	19 (3.9)	17 (4.8)	1 (5.0)	2 (1.9)
Patients using CCB at baseline, n (%)	135 (28.1)	110 (30.9)	4 (20.0)	21 (20.2)
Patients using ACEi/ARB at baseline, n (%)	144 (30.0)	118 (33.1)	4 (20.0)	22 (21.1)

Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; ECOG PS, Eastern Cooperative Oncology Group-Performance Status; IQR, interquartile range; sBP, systolic blood pressure.

(C) but also time-dependent, which suggested a long-term effect of the drug. Additionally, incorporating the cumulative area under the curve (AUC) showed lower OFV and better goodness-of-fit plots than the time after starting treatment. Therefore, both C and cumulative AUC (cumAUC) of lenvatinib were included in the model Equation 1, as a saturable effect on the increase in dBP.

$$E = \text{dBP}_{\text{base}} + \left\{ \frac{E_{\text{max}} 1 \times C}{C_{50} + C} \right\} + \left\{ \frac{E_{\text{max}} 2 \times \text{cumAUC}}{\text{cumAUC}_{50} + \text{cumAUC}} \right\} + \varepsilon \quad (1)$$

E accounts for the observed dBP (mmHg) and dBP_{base} is the baseline dBP before starting lenvatinib treatment. C accounts for the simulated concentration of lenvatinib in

plasma at the time of BP measurement ($\mu\text{g/mL}$). $E_{\max 1}$ accounts for the maximum increase in dBP (mmHg) depending on the concentration of lenvatinib. C_{50} accounts for the concentration that achieves 50% of the $E_{\max 1}$. The cumAUC is the cumulative sum of AUC ($\mu\text{g} \times \text{h/mL}$) calculated up until the time of BP measurement after starting the treatment. $E_{\max 2}$ is the maximum change in dBP (mmHg) depending on the cumAUC of lenvatinib, and cumAUC_{50} is the cumulative AUC value that achieves 50% of the $E_{\max 2}$.

The interindividual variability for $E_{\max 1}$ and $E_{\max 2}$ were described by an additive error model. The interindividual variability for C_{50} and cumAUC_{50} were described by an exponential error model. The ε accounts for the residual error, which was described by a combined additive and proportional error model.

PK/PD model and clinical factors affecting the increase in dBP

The final model was described as the following Equation 2 (model AC):

$$E = \text{dBP}_{\text{base}} + \frac{E_{\max 1} \times C}{C_{50} + C} + \frac{E_{\max 2} \times \text{cumAUC}}{\text{cumAUC}_{50} + \text{cumAUC}} - \text{ACEAR}_{\text{borCCB}} \cdot e^{(\theta \text{ACEAR}_{\text{borCCB}} + \eta \text{ACEAR}_{\text{borCCB}})} \quad (2)$$

The parameter estimates of this model using an E_{\max} model are presented in Table 2. The maximum increase in dBP based on the concentration of lenvatinib was 18 mmHg. The concentration of lenvatinib at which 50% of the maximal increase in dBP was reached was 0.09 $\mu\text{g/mL}$. No clinical factors were found to influence the increase in dBP among demographic data or clinical laboratory data. However, the baseline level of dBP suggested influence on the change in dBP (i.e., lower baseline dBP was associated with higher $E_{\max 1}$ and $E_{\max 2}$). Both model A and model C were statistically significant in the univariate analysis for describing the antihypertensive condition. However, when both A and C models were simultaneously included in the model, through multivariate analysis, the model was not statistically significant. When model AC was tested, the effect was statistically significant; thus, we selected the model AC to best describe the antihypertensive effect.

TABLE 2 Parameter estimates of the exposure-response model for the time course of increase in dBP

Parameter (units)	Estimate	Bootstrap			Shrinkage
		Median	SE	95% CI (P2.5, P97.5) ^a	
$\theta E_{\max 1}$ (mmHg)	18.17	18.39	5.005	14.06, 36.28	
θC_{50} (mg/L = $\mu\text{g/mL}$)	0.0898	0.0951	0.0457	0.0527, 0.153	
$\theta \text{dBP}_{\text{base}1}$	-1.861	-1.870	0.280	-2.385, -1.262	
$\theta E_{\max 2}$ (mmHg)	1.830	1.824	0.316	1.232, 2.580	
$\theta \text{cumAUC}_{50}$ (h)	26.66	26.81	10.86	11.71, 51.78	
$\theta \text{dBP}_{\text{base}2}$	-6.345	-6.287	0.421	-7.253, -5.481	
$\theta \text{ACEAR}_{\text{borCCB}}$	-4.537	-4.374	0.564	-5.409, -3.257	
$\sigma_{\text{prop}}^{\text{b}}$	0.0541	0.0493	0.0283	0.000504, 0.1031	
$\sigma_{\text{add}}^{\text{b}}$	7.444	7.610	1.478	2.660, 8.752	
$\omega^2 E_{\max 1}$	132.84	144.79	95.33	69.15, 430.12	0.4202
$\omega^2 C_{50}$	0.0186	0.0212	0.00546	0.00843, 0.0365	0.8200
$\omega^2 \text{dBP}_{\text{base}1}$	0.503	0.436	0.202	0.154, 0.787	0.8658
$\omega^2 E_{\max 2}$	85.23	87.58	11.85	66.72, 114.48	0.1619
$\omega^2 \text{cumAUC}_{50}$	3.862	3.970	0.879	2.368, 5.519	0.5936
$\omega^2 \text{ACEAR}_{\text{borCCB}}$	22.63	20.31	5.057	7.815, 28.06	0.8906

Abbreviations: CI, confidence interval; cumAUC, cumulative area under the curve; dBP, diastolic blood pressure; E_{\max} , maximum effect.

$$\text{Final model: } E = \text{dBP}_{\text{base}} + \frac{\left\{ E_{\max 1} \times \left(\frac{\text{dBP}_{\text{base}}}{\text{dBP}_{\text{median}}} \right)^{\theta \text{dBP}_{\text{base}1}} \right\} \times C}{C_{50} + C} + \frac{\left\{ E_{\max 2} \times \left(\frac{\text{dBP}_{\text{base}}}{\text{dBP}_{\text{median}}} \right)^{\theta \text{dBP}_{\text{base}2}} \right\} \times \text{cumAUC}}{\text{cumAUC}_{50} + \text{cumAUC}} - \text{ACEAR}_{\text{borCCB}} \cdot e^{(\theta \text{ACEAR}_{\text{borCCB}} + \eta \text{ACEAR}_{\text{borCCB}})}$$

E: observed dBP value, dBP_{base} : dBP baseline value, $\text{dBP}_{\text{median}}$: median value of dBP_{base} , $E_{\max 1}$: maximum effect of lenvatinib on dBP increase, C_{50} : lenvatinib average concentration that results in 50% of $E_{\max 1}$, $E_{\max 2}$: maximum effect of lenvatinib area under the concentration-time curve on dBP increase, cumAUC_{50} : lenvatinib cumulative AUC that results in 50% of $E_{\max 2}$, $\text{ACEAR}_{\text{borCCB}}$: categorical variable showing the use of ACEi/ARB or CCB drugs. Equal to 1 if the patient took any of these antihypertensives, or zero otherwise, $e^{(\theta \text{ACEAR}_{\text{borCCB}} + \eta \text{ACEAR}_{\text{borCCB}})}$: direct antihypertensive effect of antihypertensive treatment of either ACEi/ARB or CCB use. The variance of η is expressed as $\omega^2 \text{ACEAR}_{\text{borCCB}}$.

^aCI, P2.5, P97.5: confidence interval, 2.5th percentile, 97.5th percentile, respectively.

^b σ_{prop} , σ_{add} : SDs of proportional and additive error of combined intra-individual error model, respectively.

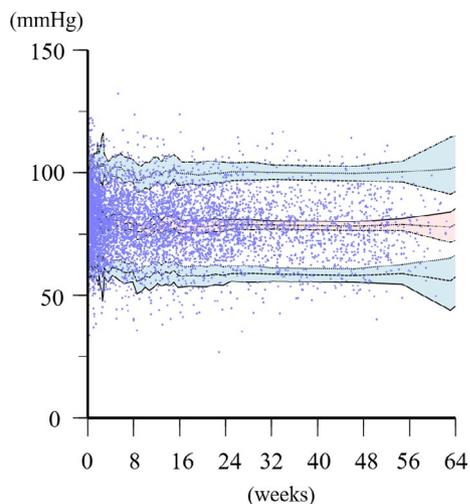


FIGURE 2 Visual predictive check of observed and model-predicted change in dBP after exposure to lenvatinib. Purple dots represent individually observed dBP. Blue shades represent predicted dBP. Each shade is the 95% CI of the 5th, 50th, and 95th percentile lines. Black line represents observed dBP of the 5th, 50th, and 95th percentiles. CI, confidence interval; dBP, diastolic blood pressure

The observed time course for change in dBP was well-described by the developed exposure-response model. Moreover, it was confirmed by robust parameter estimation, visual predictive checks, and goodness-of-fit plots (Figure S2). The visual predictive checks showed that the simulated dBP values were consistent with the observed dBP values during treatment with lenvatinib (Figure 2).

Similarly, the stability and robustness of the obtained PD parameters were confirmed using a bootstrap method. A total of 200 bootstrap runs reached successful convergence, and the bootstrap mean/final estimate ratio was within a reasonable range (Table 2).

Antihypertensive Effect of ACEi/ARB or CCB

The antihypertensive effect was expressed by an exponential treatment effect of $e^{(\theta_{ACEARBorCCB} + \eta_{ACEARBorCCB})}$ (Equation 2). The categorical variable of $ACEARBorCCB_{use}$ was equal to 1 if the patient took any of these antihypertensives, or zero otherwise. The distribution of the antihypertensive effect among individuals are shown in the histogram plot, showing high individual variability being observed in the total population (Figure 3).

Simulating the safety profile of different dosing regimens

The currently approved initial dose of lenvatinib for the treatment of thyroid cancer is 24 mg once daily. Simulations

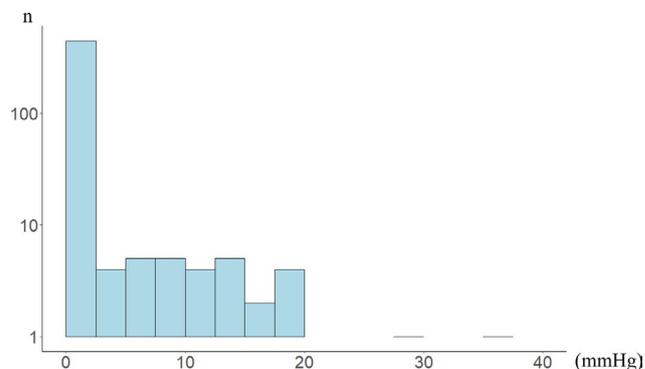


FIGURE 3 Histogram plot of the direct hypotensive effect of ACEi/ARB or CCB (480 patients). The histogram plot demonstrates the antihypertensive effect of ACEi/ARB or CCB. The antihypertensive effect was calculated using a post-hoc estimate in 480 patients. ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker

comparing the increase in dBP over 16 weeks in 3 different starting regimens (i.e., 24, 20, and 14 mg/day; Figure 4a) showed that the increase in dBP caused by the 24 mg dosing regimen was well tolerated in patients with a 60 mmHg baseline dBP (Table 3). However, this dose likely led to increased occurrence of grade 3 HTN in patients with a 90 mmHg baseline dBP (Table 3, Figure 4b,c), requiring both antihypertensive treatment and dose reduction to control the level of dBP below grade 3 HTN (Table 3).

DISCUSSION

In the present study, we developed a novel exposure-response model for lenvatinib-induced HTN using real-world PMS data. Previous PopPK/PD analyses of lenvatinib-associated HTN were based on data obtained from premarketing clinical trials, which had strict eligibility criteria and treatment schedules.^{9,10} On the other hand, our model describes the safety profile of lenvatinib in the real-world setting. Pharmacometric analysis using the PMS data enabled us to gain a mechanistic insight regarding quantitative and causal relationships between drug exposure and toxicity in patients with a variety of backgrounds. Once we have developed a well-described pharmacometric model, we are able to make a “prediction” of a future situation or situations that were not intensively observed, by means of model-based simulations. These advantages clearly show superiority of the pharmacometric approach over the classical PMS safety data analysis.

The present study showed three important findings. First, lenvatinib-induced HTN strongly correlated with the exposure of lenvatinib, as shown by the direct E_{max} model. This relationship was observed in higher occurrence of TE-HTN grade ≥ 3 HTN when starting with the standard 24 mg

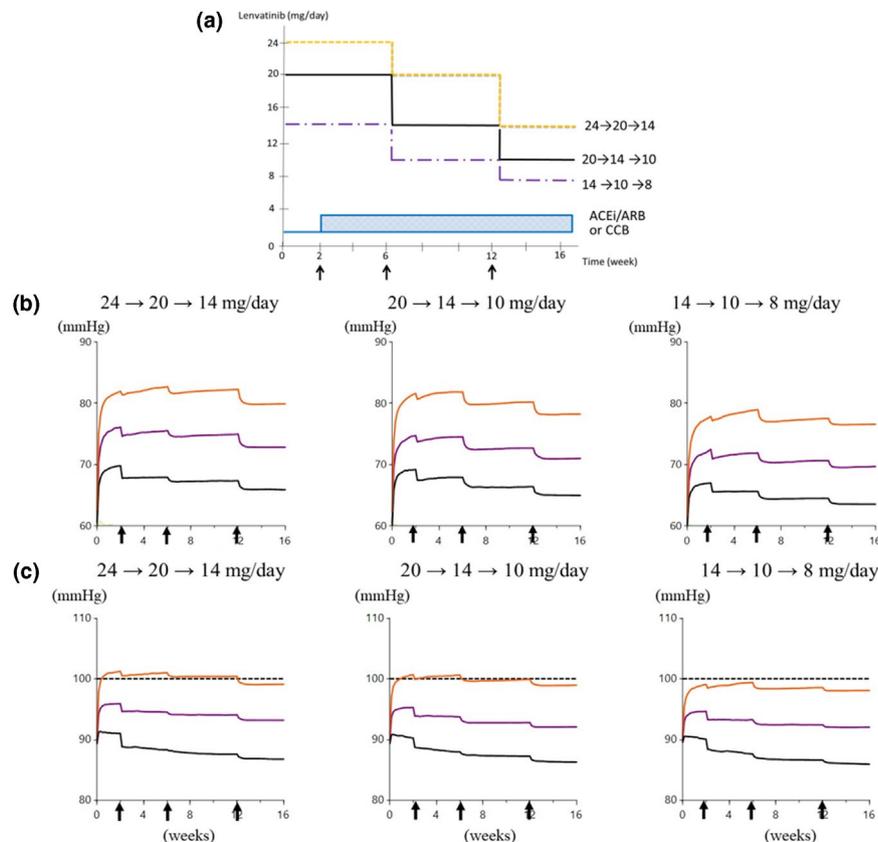


FIGURE 4 Graphical image of change in the dosing regimen and antihypertensive treatment during 16 weeks of therapy and simulated change in dBP from baseline over 16 weeks for different regimens (1000 simulations). The figure corresponds to the simulated data shown in Table 3. (a) Each black arrow (↑) represents the initiation of treatment with ACEi/ARB or CCB at week 2 and dose reduction at week 6 and week 12. Blue shade represents the use of ACEi/ARB or CCB from week 2. Orange dashed line represents the lenvatinib dosing regimen of 24 → 20 → 14 mg/day; each change in dose performed at week 6 and week 12. Black line represents the lenvatinib dosing regimen of 20 → 14 → 10 mg/day; each change in dose was performed at week 6 and week 12. Purple dot and dashed line represent the lenvatinib dosing regimen of 14 → 10 → 8 mg/day; each change in dose was performed at week 6 and week 12. (b) Change in dBP according to dose change in a patient with baseline dBP of 60 mmHg. (c) Change in dBP according to dose change in a patient with baseline dBP of 90 mmHg. Black line represents the 25th percentile. Purple line represents the 50th percentile. Orange line represents the 75th percentile. Black dotted line represents grade 3 hypertension (dBP ≥ 100 mmHg) according to the CTCAE version 4.0. ACEi/ARB or CCB was used at week 2, the dose of lenvatinib was decreased at week 6 and week 12, and dose reduction was conducted sequentially (i.e., 20, 14, 10, and 8 mg/day). Each black arrow (↑) represents the initiation of treatment with ACEi/ARB or CCB at week 2, and dose reduction at week 6 and week 12. ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; dBP, diastolic blood pressure

dose than reduced doses in simulated patients (Table 3). In the PMS data set, 32.7% of the study population experienced TE-HTN compared with 41.8% of the Phase III trial.⁴ When we examined the 90 mmHg dBP baseline cases, the chance of developing grade greater than or equal to 3 HTN at week 8, after initiation of treatment with ACEi/ARB or CCB at week 2 and one dose level reduction of lenvatinib at week 6 was as high as 26.4% (Table 3, Figure 4). Therefore, the percentage represented in the simulation is compatible with the actual PMS data set (32.7%), demonstrating a strong exposure-response relationship also in the real-world setting. The management of TE-HTN is one of the most significant aspects of the overall clinical management strategy for patients receiving lenvatinib. Predicting

the probability of developing TE-HTN and the effect of antihypertensive medications is essential to ensure optimal management of treatment with lenvatinib. A previous study compared the influence of TE-HTN on progression-free survival and overall survival.¹⁹ The simulation conducted in our current study indicates the importance of comparing the baseline level of dBP to predict the likelihood of developing TE-HTN in each patient. This will allow clinicians to take preventive measures against forthcoming HTN adverse events.

Second, our study is the first PopPK/PD analysis regarding the effect of concurrent antihypertensive treatment (i.e., ACEi/ARB and CCB). In the SELECT trial, antihypertensive medication was administered to 68% of patients treated

TABLE 3 Simulated increase in dBP according to the allotted dose regimen and proportion of patients with grade 3 hypertension (1000 simulations)

Baseline dBP (mmHg)	Lenvatinib dosing regimen (mg/day)	Median dBP [IQR] (mmHg) Patients with grade 3 HTN (%) ^a			
		Before first dose reduction at week 2 without ACEi/ARB or CCB	Before first dose reduction at week 2 with ACEi/ARB or CCB	After first dose reduction at week 6 with ACEi/ARB or CCB	After second dose reduction at week 12 with ACEi/ARB or CCB
60	24 → 20 → 14	76.7 [70.0–82.9] (1.6)	75.2 [67.8–82.1] (1.3)	74.7 [67.2–81.9] (0.9)	72.8 [65.9–79.8] (0.6)
90	24 → 20 → 14	96.2 [90.7–101.8] (31.8)	94.6 [88.6–100.8] (27.7)	94.1 [87.8–100.4] (26.4)	93.2 [86.8–99.1] (22.4)
90	20 → 14 → 10	95.2 [89.9–101.4] (29.4)	93.9 [88.3–100.5] (26.6)	92.8 [87.4–99.7] (23.7)	92.1 [86.4–98.9] (20.7)
90	14 → 10 → 8	94.7 [89.8–99.9] (24.6)	93.3 [88.1–99.0] (21.7)	92.5 [86.8–98.4] (20.0)	92.0 [86.1–98.1] (18.8)

The dBP change was simulated for 16 weeks following initiation of lenvatinib treatment with or without adding ACEi/ARB or CCB at week 2, followed by twice dose reduction at week 6 and week 12, respectively. Table shows the simulated dBP and probability of developing grade 3 HTN in virtual patients with baseline dBP of 60 mmHg or 90 mmHg with various dosing regimen. The dBP value is calculated 2 weeks after ACEi/ARB or CCB treatment (week 4) and two consecutive dose reductions (week 8 and 14) to ensure the maximum effect of each intervention.

Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; dBP, diastolic blood pressure; E_{max} , maximum effect; HTN, hypertension; IQR, interquartile range.

^aThe probability of developing Grade 3 HTN was calculated by frequency of Grade 3 HTN (dBP \geq 100 mmHg) divided by total number of simulation (i.e., $\frac{16}{1000} = 1.6$ % chance of having grade 3 HTN at week 4 in patient group with baseline dBP 60 mmHg, starting with 24 mg/day, without use of ACEi/ARB or CCB at week 2).

with lenvatinib.⁴ In our PMS data, 52% of lenvatinib-treated patients had newly received antihypertensive treatment with ACEi/ARB or CCB, and this percentage was consistent with that reported in the previous trial. Our data did not permit to evaluate the effect of diuretic therapy due to the insufficient number of patients treated with this modality.

Antihypertensive treatment at week 2 reduced the likelihood of developing TE-HTN in all regimen scenarios in both 60 and 90 mmHg dBP baseline groups. Additionally, coupled with dose reduction of lenvatinib dosing regimen at week 6 in 1000 times simulation, antihypertensive treatment reduced the probability of developing grade greater than or equal to 3 HTN in the same standard regimen at week 8, even with the same dose reduction (Table 3).

A higher incidence of severe HTN after treatment with lenvatinib was reported compared with that noted for other VEGFR inhibitors.^{19,20,21,22} This observation may be attributed to more potent inhibition of VEGFR2. By interrupting the endothelial cell survival signaling, this inhibition leads to apoptosis and capillary rarefaction in the blood capillary endothelium and an increase in vascular resistance.²⁰ Touyz et al.²³ demonstrated that VEGFR inhibition-related HTN is mediated by multiple pathways including endothelin-1 hyperactivation, nitric oxide suppression (these two are related to ACEi/ARB inhibitors), and calcium channel inhibition (CCB allows calcium channel ion activation, leading to decreased calcium ion, increasing vasodilation). Both ACEi/ARB and CCB play an important role in antihypertensive

management, easing the VEGFR inhibitor-induced hypertensive side effect.

Interestingly, when the antihypertensive effect was described in the histogram plot (Figure 3), some patients showed stronger effects than others, indicating high individual variability in the antihypertensive drug effect (Figure 3). Covariate factors, including demographic data and laboratory data, were investigated to identify the heterogeneous features of the antihypertensive effect. However, no factors for the antihypertensive effect were found. Our study did not allow us to speculate on the different antihypertensive effects between individuals, and it may be due to individual variability in the strength of nitric oxide suppression and calcium channel inhibition effect.²³ Further studies are warranted to clarify this variability.

Finally, this study found that baseline dBP and exposure to lenvatinib are key factors for lenvatinib-induced increase in dBP. In patients with low baseline dBP, it is more likely that treatment and dosage accumulation will markedly increase the dBP. As previously mentioned, there were no other risk factors found in background information and laboratory data. This could be because, even in a septuagenarian population such as that examined in our study, the performance status level was satisfactory without other serious comorbidities, resulting in a uniform population. This study is the first PopPK/PD analysis of lenvatinib using PMS data that investigated the exposure-response relationship and simulated the antihypertensive effect. In a recent

report by the US Food and Drug Administration, experts are considering to adapt real-world evidence for complementing the knowledge gained from traditional clinical trials (in which limitations render generalization to clinical practice difficult).²⁴ A prominent example is the PMS data safety management analysis performed by Kawamura et al.²⁵ By using a mechanistic PD model of eribulin-induced neutropenia, Kawamura et al. gained insight into the importance of treatment regimen selection. Our results reflect a real-world setting, in which follow-up intervals, dosing schedules, and preventive safety measures are tailored to each patient.

This analysis had several limitations due to its exploratory nature of the data. The PMS dataset was not designed to examine the causal relationship between TE-HTN and exposure to lenvatinib (i.e., TE-HTN was a post-treatment event). The dataset recorded only the date of events without the time and hours; thus, we assumed the lenvatinib administration, dBP measurement and antihypertensive treatment events occurred at the same time of each event day. This could result in limitation to estimate an exact size of the exposure-response relationship and the antihypertensive effect of ACEi/ARB or CCB. However, by synchronizing the drug exposure, dBP measurement, and antihypertensive treatment, we were able to represent the antihypertensive effect of ACEi/ARB or CCB by means of an exponential treatment effect model ($e^{\theta_{ACEi/ARB} + \eta_{ACEi/ARB}}$). The entire post hoc distribution of $e^{\theta_{ACEi/ARB} + \eta_{ACEi/ARB}}$ in 480 patients is shown in Figure 3. Additionally, the actual doses of antihypertensive treatment were not recorded in the case report form. Therefore, the analysis of antihypertensive treatment was limited to categorical classification.

In conclusion, BP data collected by PMS were successfully applied to a model-based safety analysis of lenvatinib in patients with unresectable thyroid tumors. Our study showed that baseline dBP and exposure to lenvatinib were significantly correlated with lenvatinib-induced HTN. We also observed the antihypertensive effect of treatment with ACEi/ARB or CCB. Virtual simulations of the severity of HTN were performed under different baseline dBP levels and different treatment scenarios. When the baseline dBP reaches 90 mmHg, physicians should be aware of the possibility of developing TE-HTN, and preventive use of ACEi/ARB or CCB can be considered. This analysis of real-world safety data reflecting authentic clinical settings provides useful information regarding the safety profile of lenvatinib.

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CONFLICT OF INTEREST

The authors declared no competing interest for this work.

AUTHOR CONTRIBUTIONS

Y.O., H.K., and Y.T. wrote the manuscript. Y.T. designed the research. Y.O., H.K., and Y.T. performed the research. Y.O., H.K., and Y.T. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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