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Incidence and risk factors for nausea during oral lenvatinib treatment: a single-institution nested case-control study

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Abstract

Background

Lenvatinib is an oral anticancer agent with moderate-to-high emetogenic risk and causes nausea; however, evidence for the associated symptoms and risk factors is limited. This study aimed to investigate the nausea onset characteristics in lenvatinib-treated patients and identify the risk factors for nausea.

Methods

A single-institution, nested case-control study was conducted in 161 lenvatinib-treated patients at Mie University Hospital between March 10, 2014, and March 31, 2024. The primary outcome was nausea development during lenvatinib administration; it was graded per the Common Terminology Criteria for Adverse Events, version 5.0. To evaluate the association between concomitant opioid analgesic use and the occurrence of nausea, 1:1 propensity score matching was performed, and the proportions of patients receiving concomitant opioid analgesics were compared between the case and control groups. Multivariable logistic regression analysis was performed as a sensitivity analysis in the propensity score-matched cohort.

Results

Prophylactic antiemetics were prescribed to 13 subjects (8.07%); 12 received dopamine D_2 antagonists and one received dexamethasone. Nausea was observed in 41 (25.5%) patients, and its severity was classified as grade 2 in 31 and as grade 3 in 10. The median time to onset was 32 days. In the case group, significant differences were observed in sex (p = 0.0109), height (p = 0.00230), body weight (p = 0.0104), body surface area (p = 0.00330), and concomitant opioid analgesic use (p = 0.0304) before propensity score matching. Even after 1:1 propensity score matching, the rate of concomitant opioid analgesic use in the case group was significantly higher (case group: 8/38, 21.1% vs control group: 2/38, 5.26%; p = 0.0417). Multivariate logistic regression analysis identified concomitant opioid analgesic use as an independent risk factor for nausea (adjusted odds ratio = 4.56, p = 0.0461).

Conclusions

Emetogenic risk appears to be higher in patients receiving concomitant opioid analgesics, thereby highlighting the importance of close monitoring. These findings suggest that the intensification of antiemetic therapy may be warranted in high-risk patients receiving opioid analgesics. However, further investigations are needed to confirm these findings and validate this treatment strategy.

Background

Lenvatinib, an oral multi-kinase inhibitor, has been widely used in clinical settings as first-line therapy for anaplastic thyroid cancer,[1)] unresectable or metastatic renal cell carcinoma,[2)] and hepatocellular carcinoma.[3)] Adverse events have been reported as one of the primary reasons for the discontinuation of oral multikinase inhibitors.[4)] In particular, a systematic reviews and meta-analyses revealed that lenvatinib may be associated with a higher incidence of nausea and vomiting compared to placebo,[5)] indicating that appropriate management of nausea and vomiting during lenvatinib treatment is crucial for ensuring treatment continuity.

In an international phase III trial for thyroid cancer, loss of appetite (50.2%) and nausea (41.0%) were reported to be associated with lenvatinib treatment. Another international phase III trial reported that patients with unresectable hepatocellular carcinoma who had not received previous systemic chemotherapy experienced loss of appetite (25.6%) and nausea (13.4%).[6)] Considering these findings, the emetogenic risk associated with lenvatinib is classified as high/moderate in the National Comprehensive Cancer Network (NCCN)[7)] guidelines for daily doses of ≥ 12 mg. Furthermore, the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology[8)] and the American Society of Clinical Oncology[9)] classify the risk as high/moderate regardless of the lenvatinib dose, and the 2023 Japan Society of Clinical Oncology Clinical Practice Guidelines update for antiemesis[10)] classifies the risk as moderate. However, no effective antiemetic therapy has been established for oral anticancer drugs with high/moderate emetogenic risk.[7–10)]

Recently, nausea control has been increasingly recognized as an important aspect of anticancer therapy.[10)] Although prophylactic antiemetic therapy is generally guided by clinical practice guidelines, its implementation is often individualized based on patient characteristics and circumstances in clinical settings. Identifying patient populations at high risk of nausea is essential for optimizing the selection and implementation of antiemetic therapy. In the case of lenvatinib, in particular, antiemetic use is essential for maintaining medication adherence, and standardization of this approach is required. A history of chemotherapy-induced nausea and vomiting (CINV) due to previous treatment is associated with the development of nausea and vomiting on using trifluridine/tipiracil, an oral anticancer drug classified as having high or moderate emetogenic risk.[11)] Since lenvatinib is primarily used as first-line therapy,[1–3)] there are many cases where the history of CINV cannot be assessed. Therefore, it is necessary to investigate the risk factors specific to lenvatinib; however, the evidence in this regard is limited. Hence, the present study aimed to investigate the characteristics of nausea onset in lenvatinib-treated patients and to identify the risk factors for nausea.

Methods

Study design and participants

This was a single-institution, nested case-control study and included patients aged ≥18 years who received lenvatinib treatment at Mie University Hospital between March 10, 2014, and March 31, 2024. The exclusion criteria were as follows: 1) cases for which the entire treatment period could not be ascertained; 2) Cases in which treatment was initiated or continued at other institutions; 3) cases in which the lenvatinib dose was ≤4 mg/day; and 4) cases for which test results or information necessary for the primary evaluation could not be obtained.

Definition of outcomes

The primary outcome was nausea development during lenvatinib administration. Nausea was selected as the primary outcome because some patients were receiving antiemetic therapy and few episodes of vomiting were expected, and it was assumed that all episodes of vomiting would be accompanied by nausea. Data on nausea development were collected from electronic medical records based on entries made by physicians, pharmacists, and nurses. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events version 5.0.[12)] In addition, because mild nausea (Grade 1) is difficult to assess reliably, only cases of Grade ≥2 nausea were included in the analysis. The observation period was defined as up to 90 days after lenvatinib treatment initiation based on the maximum interval between outpatient visits.

Data collection

Patient information and data on the antiemetic agents used at the start of lenvatinib treatment were collected retrospectively. Because the development of nausea on using oral anticancer drugs may be associated with a history of CINV,[11)] concomitant use of opioid analgesics,[13)] and radiation therapy,[14)] these factors were also investigated. A history of CINV was defined as nausea development immediately preceding the administration of the treatment. Data on whether opioid analgesics were newly initiated or their dosage increased during the lenvatinib treatment period were also collected.

Statistical analysis

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as median (minimum–maximum) values. Regarding the univariate analysis of continuous variables, an unpaired t-test was performed for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. For nominal variables, chi-square or Fisher's exact tests were used depending on whether any cell in the 2 × 2 contingency table had an expected count of <5.

To evaluate the impact of concomitant opioid analgesics on the development of nausea during lenvatinib administration while minimizing the effects of patient baseline imbalances, propensity score (PS) matching was performed between the case and control groups. The PS was calculated from factors

such as sex, height, and body weight, based on univariate analysis. The control and case groups were caliper matched 1:1 (0.2 of the standard deviation of the logit of the PS). After PS matching, the respective baseline patient characteristics were evaluated, and standardized differences were calculated. Because some covariates remained imbalanced after PS matching (standardized mean difference: >0.1), multivariable logistic regression analysis was performed as a sensitivity analysis to assess the robustness of the association between concomitant opioid analgesic use and nausea development during lenvatinib treatment. The development of nausea was included as the dependent variable, and factors associated with CINV[15)] and concomitant opioid analgesic use were included as explanatory variables. Multicollinearity was assessed using the variance inflation factor (VIF), and model fit was verified using the Hosmer-Lemeshow test with a *p*-value of > 0.05. Statistical analyses were performed using JMP® Student Edition version 18.2.2 (SAS Institute, Cary, NC, USA).

Ethics approval and consent to participate

This study was conducted in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol was approved by Mie University Hospital (approval number: H2024-068). Study information was disclosed on the institutional website, and informed consent was obtained using an opt-out approach, providing patients with the opportunity to decline participation.

Results

Patients

During the study period, 171 patients received lenvatinib. In accordance with the exclusion criteria, 10 patients were excluded, leaving 161 patients for the analysis (Fig. 1).

Outcome

Figure 2 shows the number of patients who experienced nausea and the time of nausea onset. Of the 161 patients, 41 (25.5%) experienced nausea. In cases where nausea was observed on day 90, medical records confirmed a diagnosis of “nausea caused by lenvatinib” by the attending physician. Of the 41 patients who experienced nausea, 31 were classified as having experienced grade 2 nausea and 10 were classified as having grade 3 nausea. The median time to onset was 32 days. Prophylactic antiemetics were prescribed to 13 patients (8.07%), dopamine D_2 antagonists to 12, and dexamethasone to one. Among the patients who developed nausea, no cases were identified in which opioid analgesics were initiated or titrated within 5 days before onset.

Univariate analysis

Table 1 shows a comparison of patient characteristics at the start of lenvatinib treatment. In the case group, significant differences were observed in sex (p = 0.0109), height (p = 0.00230), body weight (p = 0.0104), body surface area (p = 0.00330), and concomitant opioid analgesic use (p = 0.0304). Among the participants, women had significantly lower body weight than men (women: 53.5 ± 1.56 kg vs. men: 63.6 ± 1.32 kg, p < 0.0001).

PS matching

After 1:1 PS matching, both the control and case groups had 38 patients each, and significant biases in patient characteristics were eliminated (Supplementary Table 1). Table 2 shows the baseline characteristics of patients in the control and case groups after PS matching. The rate of concomitant opioid analgesic use in the case group was significantly higher after PS matching (case group: 8/38, 21.1% vs. control group: 2/38, 5.26%) (p = 0.0416). No significant differences were observed in the concomitant use of prophylactic antiemetics (p = 0.744).

Multivariable logistic regression analysis

As shown in Supplementary Table 1, age (standardized difference: 0.210) and smoking history (standardized difference: 0.213) showed residual imbalance, and multivariable logistic regression analysis was conducted using age, smoking history, and concomitant opioid analgesic use. According to multivariable logistic regression analysis, concomitant opioid analgesic use (adjusted odds ratio = 4.56, 95% confidence interval: 1.02-32.1, p = 0.0461) was identified as an independent risk factor for nausea (Table 3). The VIF values for age, smoking history, and concomitant opioid use were 1.01, 1.00, and 1.01, respectively. The p-value from the Hosmer-Lemeshow test was 0.812, indicating a good model fit.

Discussion

The incidence of nausea during lenvatinib treatment was comparable to that observed in patients classified as having a moderate risk of vomiting according to various guidelines[7–10]; cases corresponding to grade 3 nausea were also observed. Notably, this is the first evidence-based report to show that patients receiving concomitant opioid analgesics may be at a higher risk for developing nausea during lenvatinib treatment.

Given that one in four patients experienced severe nausea, the importance of nausea control with lenvatinib was reaffirmed. Nausea induced by lenvatinib most frequently develops approximately one month after treatment initiation (Fig. 2). Furthermore, even in cases of nausea developing on day 90, a link to lenvatinib was indicated based on the physician’s diagnosis. This suggests that, while particular attention is required during the first month of treatment, monitoring should continue with the understanding that delayed-onset nausea may also develop.

Previous reports indicated that the occurrence of gastrointestinal symptoms associated with lenvatinib treatment is associated with high plasma trough concentrations.[16] Although lenvatinib dosing is determined according to the body weight categories for hepatocellular carcinoma, patients with lower body weights receive the same dose within each category.[17] Univariate analysis revealed that patients with lower body weight were more frequently observed in the case group (Table 1). Therefore, it was inferred that plasma lenvatinib concentrations were relatively higher in patients with lower body weight, thereby increasing the risk of nausea. This hypothesis is supported by the fact that no significant difference was observed in the initial lenvatinib dose between the two groups. Because women have lower body weights than men, female patients may have had a higher lenvatinib exposure per body weight than male patients (Table 1).

The present study suggests that concomitant opioid analgesic use may be associated with an increased nausea risk during lenvatinib administration, even after PS matching. Because concomitant opioid analgesic use remained an independent risk factor for nausea even after adjusting for age and smoking history, which are known risk factors for CINV,[15] this sensitivity analysis supports the robustness of the present findings. Opioid-induced nausea is observed at a relatively high frequency, and the risk of its occurrence is particularly high at the start of treatment administration or within 5 days of a dose increase.[18] The results indicated that no such cases were identified in the present dataset, suggesting that the influence of opioid analgesics alone on the development of nausea in this study may be limited. Serotonin released from the enterochromaffin cells in the intestinal tract plays a crucial role in the onset of nausea and vomiting.[19] An *in vitro* study using organoids rich in enterochromaffin cells reported that exposure to multi-kinase inhibitors caused excessive serotonin release.[20] Opioid analgesics induce nausea primarily through the stimulation of the vomiting center via activation of μ-opioid receptors in the chemoreceptor trigger zone of the medulla oblongata.[13] Considering this evidence, it has been speculated that lenvatinib and opioid analgesics would contribute to nausea induction through different mechanisms, resulting in an increased risk of nausea with lenvatinib when used in combination with opioid analgesics.

A multicenter prospective observational study of antiemetic prescriptions in patients receiving the moderately emetogenic oral anticancer drugs olaparib and niraparib reported a prophylactic prescription rate of 21.7%,[21] which was similarly low to that observed in this study. The NCCN Guidelines Antiemesis Version 2.2025[7] recommend initiating oral 5-HT_3 receptor antagonists or olanzapine before the start of anticancer therapy and continuing them daily for high- and moderate-risk oral anticancer drugs. Although the present study primarily consisted of patients receiving dopamine D_2 antagonists, no significant association was observed with nausea suppression. Because dopamine D_2 antagonists are recommended for patients receiving anticancer agents with minimal or low risk,[7] their antiemetic efficacy may have been insufficient in the study population.

This study had several limitations. First, this was a single-institution retrospective observational study with a limited number of cases. Because the occurrence of nausea was assessed based on routine

medical records, there may be limitations regarding the accuracy and consistency of these assessments. Second, data following the transition to outpatient care were collected primarily from the physicians' existing medical records, which may have introduced information bias in the assessment of nausea. Third, adherence to prophylactically prescribed antiemetics was not evaluated. Fourth, while the criteria for emetogenic risk in Japanese guidelines[10] are defined as "the proportion of vomiting occurring within 24 h of anticancer drug administration without the use of antiemetics," this study used nausea as an outcome measure. Consequently, mild cases (Grade 1) may have been included in the case group, raising concerns that the incidence of gastrointestinal symptoms associated with lenvatinib may have been overestimated. Although this study has several limitations, its results provide useful foundational information for planning future multicenter prospective studies aimed at more accurately assessing the incidence of nausea in clinical settings and verifying the efficacy of standardized antiemetic therapy.

Conclusions

Emetogenic risk appears to be higher in patients receiving concomitant opioid analgesics, thereby highlighting the importance of close monitoring. These findings suggest that the intensification of antiemetic therapy, including the use of 5-HT3 receptor antagonists and olanzapine, may be warranted in high-risk patients receiving opioid analgesics. However, further investigations are needed to confirm these findings and validate this treatment strategy.

Abbreviations

D_2 antagonists
Dopamine D_2 receptor antagonists
NCCN
National Comprehensive Cancer Network
CINV
chemotherapy-induced nausea and vomiting CINV
PS matching
propensity score matching
VIF
variance inflation factor VIF
5-HT_3 receptor
5-hydroxytryptamine type 3 receptor

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and the principles of the Declaration of Helsinki. The study protocol was approved by Mie University Hospital (approval number: H2024-068). Study information was disclosed on the institutional website, and informed consent was obtained using an opt-out approach, providing patients with the opportunity to decline participation.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that there are no competing interests.

Funding

Not applicable.

Authors' contributions

Conceived and designed the study: MI, YN, YA, and TI

Performed research: MI, YN, and YA

Collected data: MI

Analyzed and interpreted data: YN and YA

Writing the paper: MI, YN, YA, HK, and TI

Supervised the study: TI

All authors read and approved of the final manuscript.

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Tables

Table 1. Comparison of patient characteristics at the start of lenvatinib administration.

Factor	Control group n = 120	Case group n = 41	*p* value
Age	71 [34-91][a]	72 [43-93][a]	0.737[b]
Sex			0.0109[c]
Male, n (%)	77 (64.2)	17 (41.5)	
Female, n (%)	43 (35.6)	24 (58.5)	
Height, cm	161 ± 8.20	156 ± 7.70	0.00230[a]
Body weight, kg	59.0 [29.2-97.4]	53.0 [36.6-91.1]	0.0104[b]
Body surface area, m^2	1.62 ± 0.178	1.53 ± 0.166	0.00330[a]
Body Mass Index	23 [13-33]	22 [16-35]	0.136[b]
Alcohol consumption history, n (%)	53 (44.2)	16 (39.2)	0.566[c]
Smoking history, n (%)	63 (52.5)	19 (46.3)	0.496[c]
Starting dose of lenvatinib, mg/day	12 [4-24]	12 [4-24]	0.849[b]
Dose of Lenvatinib, mg/kg/day	0.176 [0.0615-0.669]	0.213 [0.105-0.656]	0.321[b]
Cancer type			
Hepatocellular carcinoma, n (%)	62 (51.7)	21 (51.2)	0.961[c]
Thyroid cancer, n (%)	37 (30.8)	13 (31.7)	0.917[c]
Renal cell carcinoma, n (%)	7 (5.83)	2 (4.88)	1.00[d]
Endometrial cancer, n (%)	13(10.8)	4 (9.76)	1.00[d]
Thymic carcinoma, n (%)	1 (0.833)	1 (2.44)	0.446[d]
CINV history, n (%)	14 (11.7)	7 (17.1)	0.375[c]
Concomitant use of prophylactic antiemetics, n (%)	7 (5.83)	6 (14.6)	0.0962[d]
Concomitant use of opioid analgesics, n (%)	8 (6.67)	8 (19.5)	0.0304[d]

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as median [minimum–maximum]. [a]Unpaired t-test, [b]Mann-Whitney U-test, [c]Chi-square test, [d]Fisher's exact test.

CINV history, chemotherapy induced nausea and vomiting

Table 2. Comparison of patient characteristics at the start of lenvatinib administration after PS matching.

Factor	Control group n = 38	Case group n = 38	*p* value
Age	73 [34-85]	71 [43-87]	0.445[a]
Sex			0.646[c]
Male, n (%)	19 (50.0)	17 (44.7)	
Female, n (%)	19 (50.0)	21 (55.3)	
Height, cm	157 [146-170]	157 [145-172]	0.913[a]
Body weight, kg	54.8 [42.5-80.3]	53.5 [36.6-91.0]	0.988[a]
Body surface area, m^2	1.55 ± 0.140	1.55 ± 0.158	0.963[b]
Body Mass Index	21.9 [16.3-29.8]	21.8 [15.8-34.7]	0.864[a]
Alcohol consumption history, n (%)	14 (36.8)	16 (42.1)	0.639[c]
Smoking history, n (%)	15 (39.5)	19 (50.0)	0.356[c]
Starting dose of lenvatinib, mg/day	11 [4-24]	12 [8-24]	0.923[a]
Dose of Lenvatinib, mg/kg/day	0.177 [0.0615-0.545]	0.214 [0.115-0.656]	0.685[a]
Cancer type			
Hepatocellular carcinoma, n (%)	17 (44.7)	20 (52.6)	0.491[c]
Thyroid cancer, n (%)	14 (38.8)	11 (28.9)	0.464[c]
Renal cell carcinoma, n (%)	1 (2.63)	2 (5.26)	1.00[d]
Endometrial cancer, n (%)	6 (15.8)	4 (10.5)	0.497[c]
Thymic carcinoma, n (%)	0 (0.00)	1 (2.63)	1.00[d]
CINV history, n (%)	6 (15.8)	6 (15.8)	1.00[c]
Concomitant use of prophylactic antiemetics, n (%)	5 (13.2)	6 (15.8)	0.744[c]
Concomitant use of opioid analgesics, n (%)	2 (5.26)	8 (21.1)	0.0417[c]

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as median [minimum–maximum]. [a]Mann-Whitney U-test, [b]Unpaired t-test, [c]Chi-square test, [d]Fisher's exact test

CINV history, chemotherapy induced nausea and vomiting; PS, propensity score.

Table 3. Multivariate logistic analysis of nausea during lenvatinib administration after PS matching.

	Adjusted odds ratio	95% CI	*p* value
Age	0.982	0.935 – 1.03	0.451
Smoking history	0.654	0.252 – 1.67	0.374
Concomitant use of opioid analgesics	4.56	1.02 – 32.1	0.0461

PS, propensity score; 95% CI, 95% confidence interval.

Figures

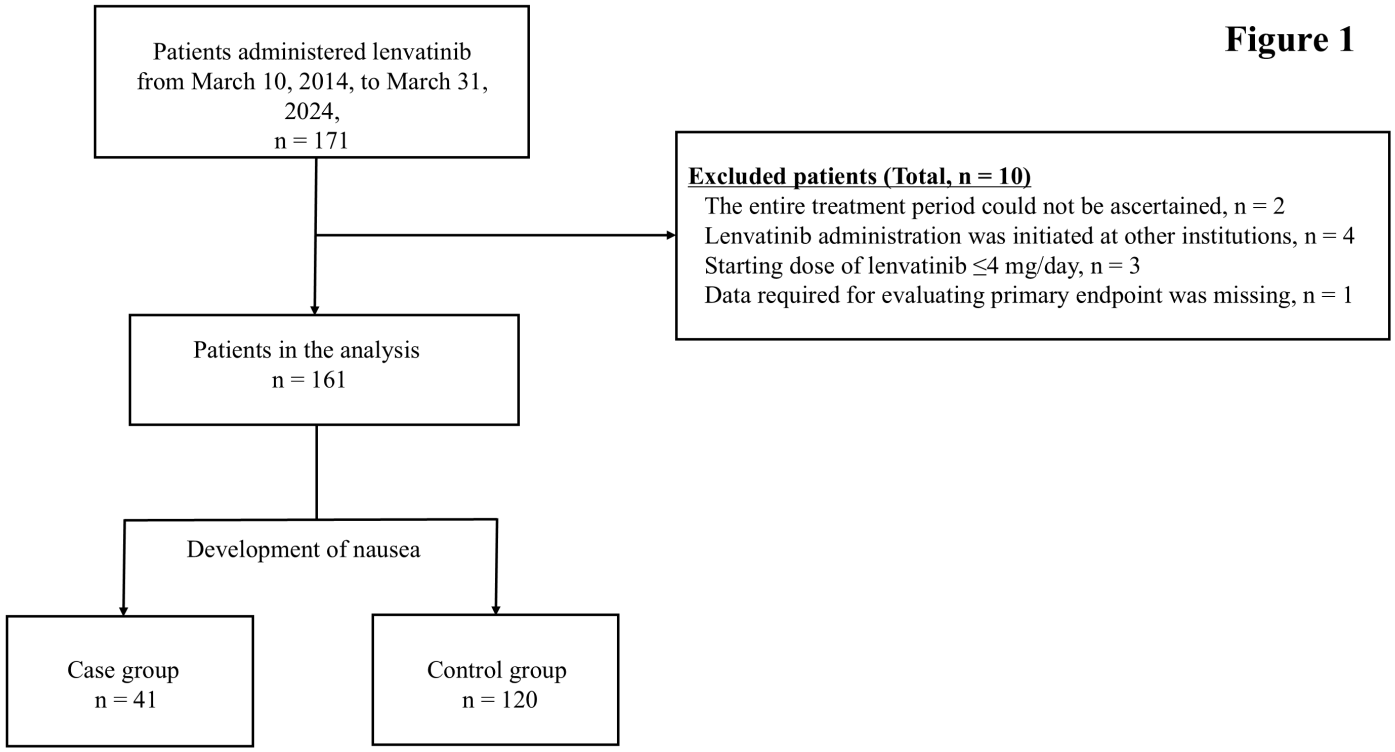


Figure 1

Flow diagram for the patient selection process.

The n represents the number of patients.

Figure 2

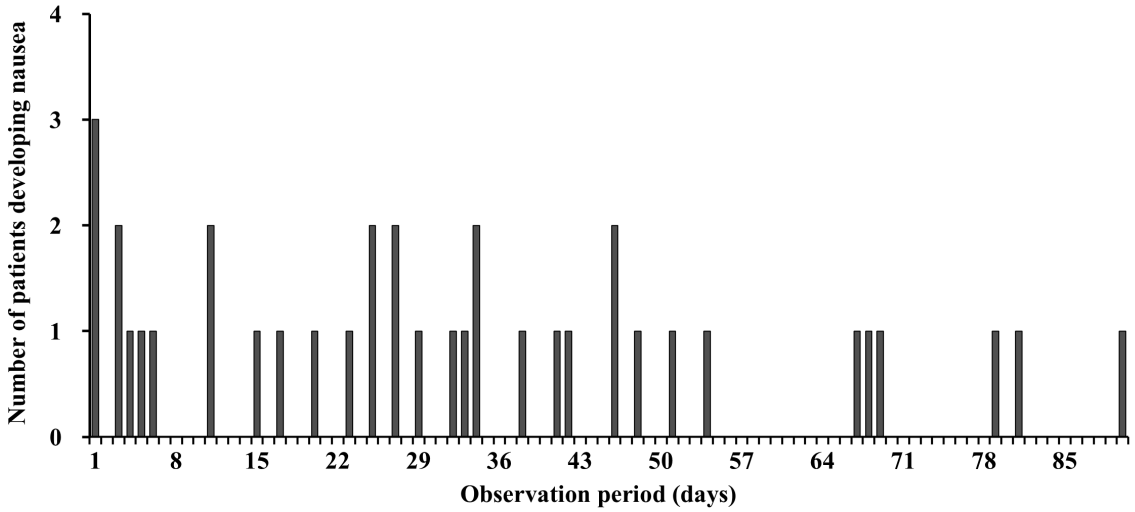


Figure 2

Time to the first onset of nausea after the initiation of lenvatinib treatment.

Although three cases of nausea were identified, the exact date of onset could not be determined.

Supplementary Files

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- Supplementarymaterials261017.docx