Pharmacokinetic/pharmacodynamic analysis of lenvatinib in patients with hepatocellular carcinoma

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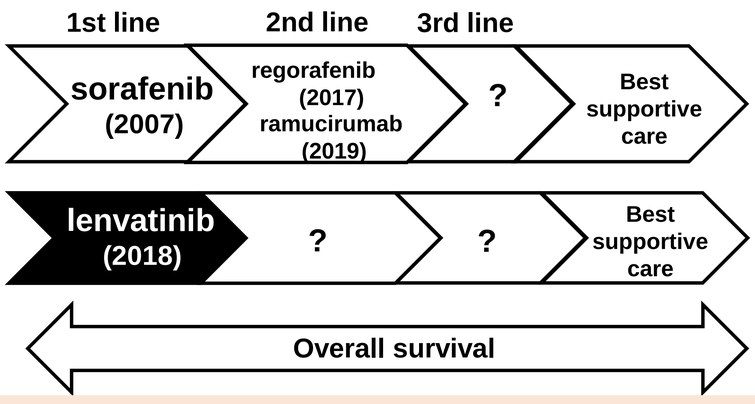
Molecular targeted agents for hepatocellular carcinoma (HCC)



Lenvatinib is the first new first-line treatment option for advanced HCC to be approved in approximately 10 years.

Lenvatinib

Mechanism
oral multi-kinase inhibitor

Usage
HCC, thyroid cancer

Standard Dosage（HCC）
12 mg/day for bodyweight ≥ 60 kg
or 8 mg/day for bodyweight < 60 kg

From the results of phase II PK study and simulated PPK study (12 mg was overdose for < 60 kg pt.)

Side effects
Hypertension, Proteinuria, Fatigue, Anorexia, Hypothyroidism

Lenvatinib showed significantly improvements in overall response rate (ORR), progression-free survival, and time to progression than sorafenib in phase III trial (REFFLECT trial).

However ・・・
Lenvatinib induces frequently severe adverse events (PIII vs. sorafenib).
grade ≥ 3 toxicities：57.0%
Dose interruption due to AEs：40.0%
Dose reduction due to AEs：37.0%

The predictive marker for toxicity or dose adjustment is needed!

Introduction

Lenvatinib has been approved as first-line therapy for advanced hepatocellular carcinoma (HCC).

Severe adverse events frequently occur in patients treated with lenvatinib, necessitating dose reduction and discontinuation.

However, information on the exposure-toxicity /efficacy relationship is limited.

Purpose

The aim of the current study was thus to evaluate the association of lenvatinib-induced toxicities and clinical outcomes with the pharmacokinetics in patients with HCC.

Conclusion

Lenvatinib shows a large inter-patient variability in trough conc. in HCC pt., even though lenvatinib was treated with dosage based on body weight.

We also showed that lenvatinib of ≥ 55.2 ng/mL led to severe toxicity in patients with HCC.

Dose reduction or temporary discontinuation might be needed, when lenvatinib conc. is ≥ 55.2 ng/mL, in order to avoid its severe toxicities.

Methods

Study design
Retrospective and observational clinical study

Patients
HCC patients treated with lenvatinib
(12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg)

Study period
August 2018 to March 2019 (Patients enrollment)
The cutoff date for this analysis was June 30, 2019.

PK assessment
Trough conc. in a steady state (day ≥7) at each visit

Toxicity assessment
The trough lenvatinib conc. was assessed for the sample closest in time to the occurrence of lenvatinib-induced toxicity. All toxicities were assessed according to CTCAE v.4.

Clinical outcome assessement
The association of the median lenvatinib conc. for first 3 months after lenvatinib initiation with objective response rate was assessed. Tumor assessment using CT or MRI was performed every 6–8 weeks. The best tumor response was assessed using the mRECIST guidelines for HCC.

HPLC measurement condition for lenvatinib conc.

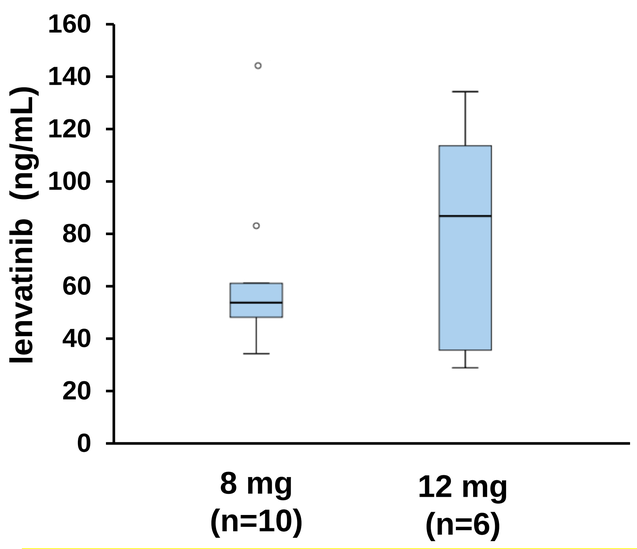
Preparation
After deproteinization, it was filtered with a filter having a pore size of 0.45 μm to obtain a sample for analysis.

HPLC condition
Mobile phase: 10 mM phosphate buffer (pH 6.9) / acetonitrile (72: 28)
Flow rate: 1.0 ml/min
UV detection: 244 nm
Injection volume: 50 μl
Temprature: 40 ˚C

Table 1 Patient Characteristics

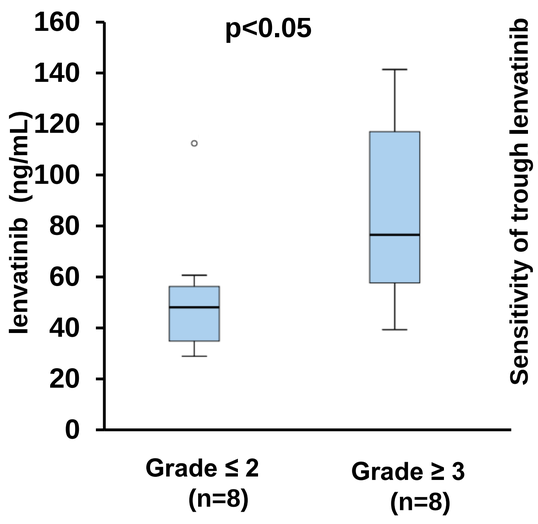
		Total n=16
Median lenvatinib concentration (ng/mL) (range)		59.4 (30.8- 143)
Age (year) median (range)		74 (60-88)
Body weight (kg) median (range)		62.5 (39.9-74.3)
Gender, n (%)	Female	2 (12.5)
	Male	14 (87.5)
Etiology, n (%)	HBV	0 (0.0)
	HCV	5 (31.3)
	NBNC	11 (68.7)
Child Pugh, n (%)	A	15 (93.8)
	B	1 (6.2)
Initial dose, n (%)	12 mg	6 (37.5)
	8 mg	10 (62.5)

HBV; hepatitis B virus, HCV; hepatitis C virus, NBNC; negative both HBV and HCV

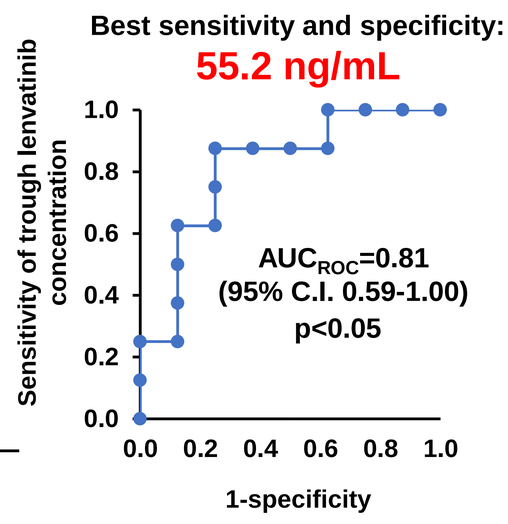


Lenvatinib showed a large inter-patient variability in trough conc., even though dosage was adopted based on body weight.

Fig. 1 Serum trough conc. of lenvatinib at an initial dosage at a steady state



Mean trough lenvatinib conc. was significantly higher in the grade ≥ 3 toxicity group than in the grade ≤ 2 toxicity group (P<0.05).



Based on the receiver operating characteristic curve, the threshold value of trough lenvatinib conc. for predicting grade ≥ 3 toxicities was 55.2 ng/mL.

Fig. 2 Trough lenvatinib threshold for grade ≥3 toxicities.

Table 2 Comparison of Grade≥3 side effects based on the lenvatinib exposure

Side effects grade ≥3	≥55.2 ng/mL (n=9)	<55.2 ng/mL (n=7)
	No. (%)	
All events	7 (77.8%)	1 (14.3%)
Hypertension	3 (33.3%)	0 (0.0%)
Anorexia	2 (22.2%)	0 (0.0%)
Proteinuria	1 (11.1%)	0 (0.0%)
Fatigue	1 (11.1%)	0 (0.0%)
Stamatitis	0 (0.0%)	1 (14.3%)

Table 3 Comparison of ORR according to lenvatinib exposure

Lenvatinib <55.2 ng/mL (n=7)	Lenvatinib ≥55.2 ng/mL (n=9)
CR : 1 (14.3%)	CR : 0 (0.0%)
PR: 4 (57.1%)	PR: 4 (44.4%)
SD: 0 (0.0%)	SD: 0 (0.0%)
PD: 1 (14.3%)	PD: 0 (0.0%)
NA: 1 (14.3%)	NA: 5 (55.6%)
ORR: 71.4%	ORR: 44.4%

CR, complete response; PR, partial reponse; SD, stable disease; PD, progression disease NA, not assessment
ORR, objective response rate

ORR between patients with < 55.2 ng/mL (n = 7) and patients with ≥ 55.2 ng/mL lenvatinib (n = 9) were not significantly different (71.4% vs. 44.4%, *P* = 0.28).

Discussion

In a PII trial of lenvatinib in HCC (Japan, Korea), all patients were treated with 12 mg[1)].

In this trial, the median trough concentrations on day 15 of cycle 1 in patients who required dose modifications and in those who did not were 62.4 and 33.0 ng/mL, respectively.

This result is similar to our result (≥60 kg 12 mg, <60 kg 8 mg), suggesting that lenvatinib ≥60 ng/mL is toxic level .

[1)]Ikeda et al., J Gastroenterol (2017) 52:512–519

Conflicts of Interest and Source of Funding:
For all authors none were declared.