The 18th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology (IATDMCT 2020)
September 13-16 | Banff, Canada

Pharmacokinetic/pharmacodynamic analysis of lenvatinib in patients with hepatocellular carcinoma

Noda S[1], Wakasugi Y[1], Yabuta N[1], Sudou M[1], Hira D[1,2], Iida H[3], Osaki R[4], Fujimoto T[4], Tani M[3], Andoh A[4], Morita SY[1], Terada T[1]

[1]Department of Pharmacy, Shiga University of Medical Science Hospital
[2]College of Pharmaceutical Sciences, Ritsumeikan University
[3] Department of Surgery, Shiga University of Medical Science Hospital
[4]Department of Gastroenterology, Shiga University of Medical Science Hospital

Background: 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. Therefore, a predictive marker for preventing its severe toxicities is needed. Lenvatinib shows a large inter-patient variability in serum concentrations. With the considerable interindividual differences in pharmacokinetics, some patients could be inadequately exposure to lenvatinib. However, information on the exposure-toxicity/efficacy relationship is limited. 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. **Methods:** For this retrospective and observational clinical study, we examined 16 patients with HCC treated with lenvatinib (12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg) and enrolled between August 2018 and March 2019. The primary goal was to evaluate the association between trough lenvatinib concentration at a steady state and occurrence of grade ≥ 3 toxicities, and secondarily, to estimate the association between trough lenvatinib concentration and objective response rate (ORR). **Results:** The median lenvatinib trough concentration was 59.4 ng/mL (range 30.8-143 ng/mL). Mean trough pazopanib concentration was significantly higher in the grade ≥ 3 toxicity group (n = 8) than in the grade ≤ 2 toxicity group (n = 8). The most common Grade ≥3 toxicities were hypertension (n=3), anorexia (n=2). Based on the receiver operating characteristic curve, the threshold value of trough lenvatinib concentration for predicting grade ≥ 3 toxicities was 55.2 ng/mL (area under the curve, 0.81; 95% confidence interval, 0.59-1.00; $P < 0.05$). ORR between patients with ≥ 55.2 ng/mL lenvatinib (n = 9) and patients with < 55.2 ng/mL (n = 7) were not significantly different (44.4% vs. 71.4%, $P = 0.28$). **Conclusions:** From results of this study, we 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 concentration is ≥ 55.2 ng/mL, in order to avoid its severe toxicities.

Key words: lenvatinib, hepatocellular carcinoma, pharmacokinetics