Poster

[P26-7] P26-7: Oncologic drugs (3): Pharmaometrics, PK/PD, special population

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[P26-7-5] Assessment of sorafenib-induced toxicities and clinical outcomes based on therapeutic drug monitoring of soarfenib for patients with hepatocellular carcinoma

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Keywords: Sorafeinb, pharmacokinetics, hepatocellular carcinoma therapeutic drug monitoring

Background

Sorafenib has been approved for the treatment of advanced hepatcellular carcinoma (HCC). Sorafenib frequently induces severe toxicities, resulting in dose reduction or discontinuation. Therefore, a predictive marker for preventing its severe toxicities is needed. Sorafenib shows a large inter-patient variability in plasma concentrations. With the considerable interindividual differences in pharmacokinetics, some patients could be inadequately expose to sorafenib. However, the benefit of pharmacokinetic assessment of sorafenib remains unknown. The aim of the current study was thus to evaluate the association of sorafenib-induced toxicities and clinical outcomes with the pharmacokinetics in patients with HCC.

Methods

A retrospective, observational clinical study was performed. Twenty-six Japanese HCC patients were enrolled between September 2010 and March 2015. The cutoff date for this analysis was March 31, 2016. After obtaining written informed consent from the patient, blood samples were collected before administration. Sorafenib was evaluated by high-performance liquid chromatography. Side effects were evaluated using the Common Toxicity Criteria for Adverse Effects v4.0. The tumor response was assessed using the Response Evaluation Criteria in Solid Tumors.

Results

Patients were started on sorafenib at doses of 800 mg (n=4), 400 mg (n=14), and 200 mg (n=8) daily. The median sorafenib concentration was 2.91 μg/mL (range 0.74-8.8 μg/mL). Sorafenib concentration significantly correlated with Grade 2 occurrence of anorexia, diarrhea, hand-foot syndrome, and rash. Patients with 4 μg/mL sorafenib (n=8), compared with patients with <4 μg/mL (n=17), had a greater incidence of Grade 2 toxicities (88.9% [n=8] vs. 41.2% [n=7]). Patients with <4 μg/mL sorafenib had significantly longer median time to treatment failure (TTF), median progression-free survival time (PFS), and median overall survival (OS) than patients with 4 μg/mL (TTF 210 vs. 43 days, P<0.01; PFS 394 vs. 86 days, P<0.01; OS 394 vs. 150 days, P<0.01).

Conclusions

This study suggests that therapeutic drug monitoring of sorafenib could be helpful for avoiding severe sorafenib-induced side effects. Sorafenib of 4 μg/mL leads to increased discontinuation due to severe toxicity, resulting in shortened TTF, PFS, and OS. Dose reduction may be needed, especially when the sorafenib concentration is above 4 μg/mL, in order to avoid unnecessary early discontinuation of treatment.