Poster

[P25-10] P25-10: Oncologic drugs (2)

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[P25-10-7] Preclinical and clinical studies on establishment of invasive marker of dihydropyrimidine dehydrogenase activity and its usefulness in 5-fluorouracil-based chemotherapy

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Background

5-Fluorouracil (5-FU) is an anticancer agent widely used in cancer chemotherapy. 5-FU is inactivated by dihydropyrimidine dehydrogenase (DPD), and its activity is supposed to correlate with pharmacokinetics/pharmacodynamics of 5-FU. This study was conducted to find an invasive marker predictive of DPD activity, and to evaluate its usefulness in 5-fluorouracil-based chemotherapy. Here, we considered the ratio of plasma concentration of dihydrouracil (UH2) to that of uracil (Ura) to be a candidate, since Ura is metabolized by DPD into UH2.

Methods

1) Preclinical study: 5-FU was infused at a dose of 200 mg/m2/4 hr, with or without a bolus injection of 5-FU (20 or 60 mg/kg) before the infusion in rats. Time-profiles of plasma concentration of 5-FU and UH2/Ura ratio were evaluated. The DPD activity was measured using isolated liver. 2) Clinical study: 28 patients with pancreatic cancer were enrolled, who were treated with modified FOLFIRINOX regimen. The plasma UH2/Ura ratio was measured prior to the treatment. The correlations with progression free survival (PFS) and overall survival (OS) were evaluated retrospectively. The study was conducted with the authorization of the institutional review board and followed the medical research council guidelines of Okayama University, Japan. Written informed consent was obtained from all participants prior to enrollment.

Results

1) Preclinical study: An addition of bolus injection of 5-FU resulted in longer half-life of 5-FU after the end of 5-FU infusion ($p<0.05$). The hepatic DPD activity was down-regulated ($P<0.05$), and plasma UH2/Ura ratio was decreased ($P<0.05$) by addition of bolus injection of 5-FU. These phenomena were observed dependently on 5-FU dose of bolus injection. 2) Clinical study: Multivariate analysis suggested that only plasma UH2/Ura ratio affected PFS. PFS was 9.3 months in patients with higher UH2/Ura ratio, but 5.0 months in those with lower ratio (boundary value of 0.3, $p = 0.002$). There was no association of OS and plasma UH2/Ura ratio.

Conclusions

Plasma UH2/Ura ratio is a marker of hepatic DPD activity and 5-FU pharmacokinetics, and might be a predictive of prognosis after 5-fluorouracil-based chemotherapy.