Oral

[O27-3] O27-3: Oncology (1)

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[O27-3-2] Development of an S-1 dosage formula based on renal function by a prospective pharmacokinetic study

Eisuke Booka[1], Chiyo K. Imamura[2], Hiroya Takeuchi[3], Yasuo Hamamoto[4], Daisuke Gomi[5], Takuro Mizukami[6], Takashi Ichiyama[7], Kazunari Tateishi[8], Tsunehiro Takahashi[9], Hirofumi Kawakubo[10], Keuzo Soejima[11], Narikazu Boku[12], Yusuke Tanigawara[13], Yuko Kitagawa[14] (1.Keio University, 2.Keio University, 3.Keio University, 4.Keio University, 5.Shinshu University, 6.St Marianna University, 7.Shinshu University, 8.Shinshu University, 9.Keio University, 10.Keio University, 11.Keio University, 12.St Marianna University, 13.Keio University, 14.Keio University)

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Background

S-1 is an oral anti-cancer drug, containing tegafur (FT), a prodrug of fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate. As renal dysfunction is known to increase exposure of 5-FU following S-1 administration, the incidence of severe adverse reactions is increased in patients with impaired renal function. However no reliable information on its dose modification for patients with renal dysfunction is provided.

Methods

We conducted a prospective pharmacokinetic study to develop an S-1 dosage formula based on renal function. Sixteen cancer patients with varying degrees of renal function received a single dose of S-1 at 40 mg/m^2. A series of blood samples were collected at predefined times over 24 h to assess the plasma concentration profiles of 5-FU, CDHP, and FT. A mathematical model for the relationship between renal function and exposure of 5-FU was constructed by a population pharmacokinetic analysis.

Results

The clearance of 5-FU following S-1 administration was related to body surface area (BSA) and creatinine clearance (CLcr) in the range of 15.9–108.8 mL/min as estimated by the Cockcroft–Gault equation. The S-1 dosage formula was derived as follows: dose = target AUC ×(21.9 + 0.375 ×CLcr) ×BSA. The recommended daily doses of S-1 in Asia and Europe were also proposed as nomograms according to exposure matching to the previously reported AUC of 5-FU, which confirmed the efficacy and toxicity in pivotal registration studies.

Conclusions

We developed a novel formula for determining the S-1 dosage based on renal function. Further validation is needed to confirm the formula for practical application.