Poster

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

Chair: Shiro Fukumori, Japan

Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall)

[P26-7-6] Meta-analytic population pharmacokinetic analysis to evaluate the effect of renal dysfunction on imatinib clearance in Japanese subjects

Sayo Suzuki[1], Yuki Hattori[2], Akinori Takagi[3], Tohru Aomori[4], Hidefumi Kasai[5], Tomonori Nakamura[6] (1.Keio University, 2.Keio University, 3.Keio University, 4.Keio University, 5.Certara G. K, 6.Keio University)

Keywords: Imatinib, population pharmacokinetics, renal dysfunction, Japanese, special population

Background

There are growing concerns about the pharmacokinetics (PK) of anti-cancer agents in specific populations. Imatinib was the first molecularly targeted anti-cancer drug to be more effectively used by therapeutic drug monitoring. The National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) reported elevated Cmax and AUC of imatinib in patients with renal dysfunction, although daily dosing was well tolerated. Recently, renal impairment due to long-term imatinib use has been reported. However, imatinib PK in Japanese patients with renal dysfunction remains unclear. This pilot study was conducted to assess the effect of renal dysfunction on imatinib PK in Japanese patients, and determine the most effective and safe dose for each patient.

Methods

A population pharmacokinetic (PPK) analysis was performed by applying a non-linear mixed-effect model using Phoenix NLME1.3. Literature search using PubMed and the Japanese database Ichushi yielded data on serum imatinib concentrations in Japanese subjects. Random number generation was used to construct 100 data sets. PPK parameters were calculated as mean ±SE. The only source of PPK parameters of imatinib in Japanese patients was a study by Yamakawa et al. (Ther. Drug. Monit. 2011), which was used as the base model for comparison.

Results

A total of 424 serum imatinib concentrations were obtained: 92 measured values, 146 graphically extracted from plots, and 186 virtual data points generated using the random number generation from actual datasets. Of these, 13 were from 3 patients with renal dysfunction: serum creatinine 1.24, mild renal dysfunction, and on dialysis. The rest with no particular mention about renal function was labeled as patients without renal dysfunction. Typical value of imatinib clearance (tvCL) was estimated as 12.2 (L/h), and imatinib clearance in patients with renal dysfunction was estimated as follows: CL=tvCL x (1-0.412), indicating decreased imatinib clearance in patients with renal dysfunction.

Conclusions

Our PPK analysis showed decreased imatinib clearance in Japanese patients with renal dysfunction, compared to that in those without renal dysfunction, supporting the results of the NCI-ODWG study. Further clinical data are required to confirm the modified PPK model in this study and establish rational imatinib dosage regimens in patients with renal dysfunction.