Poster

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

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[P26-7-3] Continuous cytostatic effects of BCR-ABL tyrosine kinase inhibitors(TKIs) after washout in human leukemic K562 cells

Tsuyoshi Aoyama[1], Mitsuru Sugawara[2], Yoh Takekuma[3], Yuki Sato[4], Masato Sumi[5] (1.Hokkaido University, 2.Hokkaido University, 3.Hokkaido University, 4.Hokkaido University, 5.Hokkaido University)

Keywords: dasatinib, nilotinib, imatinib, chronic myeloid leukemia, cell viability

Background

We have been conducting TDM of BCR-ABL tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Some patients treated with dasatinib could achieve and maintain a response, although their dasatinib serum concentrations were below the therapeutic range or the dosage schedule was twice a week. On the other hand, imatinib has been shown in several previous studies to have a poor response due to noncompliance.

These findings indicated that there are different characteristics of cell proliferation inhibition among TKIs. Hence, we examined the differences in continuous cytostatic effects of TKIs (imatinib, nilotinib and dasatinib) after washout in human leukemic K562 cells.

Materials and Methods

K562 cells were exposed to imatinib mesylate, nilotinib and dasatinib at concentrations of 2,500 ng/mL, 2,500 ng/mL and 100 ng/mL, respectively. These concentration were determined on the basis of C_{max} values after administration of TKIs in humans. After exposure for 3 hours, TKIs were adequately removed by washing with media. Thereafter, K562 cells were cultured for various periods of time. The cytotoxic effects of the TKIs on K-562 cells were determined by CCK-8 assays.

Results and Discussion

Cell viability decreased in a culture time-dependent manner after washing out the drugs [dasatinib: 59.9% (24 hr), 30.9% (48 hr), 19.6% (72 hr); nilotinib: 40.1% (24 hr), 7.87% (48 hr), 7.68% (72 hr)]. In contrast, imatinib did not decrease cell viability [88.0% (24 hr), 92.6% (48 hr), 96.8% (72 hr)]. A previous study showed that dasatinib and nilotinib induce apoptosis after washout. Thus, apoptosis may proceed without these drugs.

Conclusions

Compared with first-generation imatinib, second-generation dasatinib and nilotinib showed continuous cytostatic effects on K562 cells after washout. The results suggest that a good response in patients with a low serum concentration of dasatinib may be due to cytostatic effects of dasatinib that continue even after its disappearance in blood.