Poster

[P26-8] P26-8: Oncologic drugs (4): Pharmacokinetics, TDM practice

Chair: Kohji Naora, Japan

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[P26-8-1] Pharmacokinetics and toxicological evaluation of cyclophosphamide in mice

Emiko Miyahara[1], Takuro Nishikawa[2], Kazuro Ikawa[3], Miharu Ushikai[4], Hiroaki Kawaguchi[5], Yasuhiro Okamoto[6], Norifumi Morikawa[7], Masahisa Horiuchi[8], Yoshifumi Kawano[9] (1.Kagoshima University, 2.Kagoshima University, 3. Hiroshima University, 4. Kagoshima University, 5. Kagoshima University, 6. Kagoshima University, 7. Hiroshima University, 8. Kagoshima University, 9. Kagoshima University)

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Background

High-dose cyclophosphamide (CY) is known to cause cardiac toxicity, however, the mechanisms are poorly understood. Previously, we found in *in vitro* experiments that N-acetylsysteine (NAC) increased *o*-carboxyethyl-phosphoramide (CEPM), a CY metabolite, and decreased CY-induced cell toxicity. This study evaluated *in vivo* toxicokinetics of CY in mice.

Methods

Six-week-old female C57BL/6J mice were pretreated with NAC (200 mg/kg, i.p.) or saline once a day for 5 consecutive days. Two hours after the last dose, mice were injected with CY (500 or 700 mg/kg, i.p.) or saline. Blood was collected from the vena caudalis 1 and 3 hours after CY administration. The concentrations of CY, 4-hydroxycyclophosphamide (HCY) and CEPM in plasma were detected by liquid chromatography/tandem mass spectrometry. The area under the concentration-time curve ($AUC_{0-\infty}$) was calculated using a one-compartment model. Furthermore, 24 hours after the induction of CY, heart and liver were removed and then stained with hematoxylin and eosin.

Results

Died mice were 1 of 3 for CY 700 mg/kg (CY700) and 2 of 3 for NAC+CY700; but none for CY 500 mg/kg (CY500) and NAC+CY500. The $AUC_{0-\infty}$ for CY500 and NAC+CY500 were as follows: CY 1555 ±29 (mean ± standard deviation) and 1675 ±65, HCY 1092 ±97 and 1067 ±130, CEPM 680 ±57 and 728 ±15 mg*h/L, respectively. The $AUC_{0-\infty}$ for CY700 and NAC+CY700 were as follows: CY 4809 ±1782 and 3473 ±822, HCY 555 ±115 and 839 ±386, CEPM 1305 ±255 and 1824 ±510 mg*h/L, respectively. At 1 hour after CY administration, NAC+CY700 group showed significantly higher CEPM concentrations than CY700 group (p <0.05). No significant change was found in $AUC_{0-\infty}$ between dead and living groups. However, dead group showed higher concentrations of HCY than living group (p <0.1). At the dose of 700 mg/kg, focal degeneration and fatty deposition-like degeneration were found in hearts and livers, respectively.

Conclusions

CY induced death and pathological changes in hearts and livers at the dose of 700 mg/kg in mice. However, there were no significant differences in $AUC_{0-\infty}$ between dead and living groups.