Poster

[P26-9] P26-9: Oncologic drugs (5): Pharmacokinetics, TDM practice

Chair: Kiyoshi Mihara, Japan

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[P26-9-1] Delayed high-dose methotrexate excretion: is there any relationship with proton pump inhibitors in patients with hematological malignancy?

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Background

High-dose methotrexate (HDMTX) has been used to treat regimens for multiple malignancies. But the delayed excretion of MTX has led to drug accumulation and increased risks of systemic toxicity. This study aims to explore whether there is any potential relationship between delayed MTX excretion and combined using of proton pump inhibitors (PPIs) in patients with hematological malignancy.

Methods

A total of 186 hematological malignancy patients were treated with HDMTX chemotherapy (558 cycles) from 2015 to 2016 and for whom serial MTX plasma concentrations (C_{48h}, C_{72h} and C_{96h}) were collected. Delayed MTX excretion was defined as $C_{mtx\text{-}48h}$ 1 μM, $C_{mtx\text{-}72h}$ 0.1 μM or $C_{mtx\text{-}96h}$ 0.05 μM. Factors that may influence delayed MTX excretion (age, gender, weight, MTX dosage and the use of PPIs) were analyzed. Population and the individual MTX possible drug interaction were estimated by *multiple linear regression* and *pearson's correlation*.

Results

Despite significant differences between those receiving PPIs and not receiving PPIs in the mean MTX levels at 72h after MTX administration (1.14 vs. 0.33 μmol/l, respectively, *p<0.05)* and 96h after MTX administration (0.58 vs. 0.23 μmol/l, respectively, *p<0.05*), there is no difference between those patients in the proportion of patients experiencing delayed excretion at 48h (1.78 vs. 1.59 μmol/l, respectively, $p>0.05$). When data were analysed using multiple linear regression and pearson's correlation for multiple cycles, co-administration of PPIs was not a significant predictor of HDMTX delayed excretion at 3 time points (r= 0.014, $p=0.804$ at 48h time point; r=0.010, $p=0.888$ at 72h time point; r=0.032, $p=0.853$ at 96h time point). Interestingly, the study found that the HDMTX delayed excretion was positively correlated with the MTX dosage and negatively with weight factor, and the regression model is as follow: $Cmtx=0.444+0.163X_1-0.128X_2$ (r=0.773, $p<0.05$, X_1: the dosage of MTX;X_2: weight factor)

Conclusions

Precaution of delayed excretion of MTX is needed during hematological malignancy treatment using HDMTX. An optimal individualized rescue strategy can be created under the consideration of weight, the usage of MTX, and the combined use of PPIs. The hematological malignancy patients may need additional monitoring

to avoid toxicity.