Poster

[P27-2] P27-2: Anti-infective drugs (7): Antifungals

Chair: Yoh Takekuma, Japan

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[P27-2-10] Intermittent prophylactic high dose administration of micafungin in a cohort of children undergoing hematopoietic stem cell transplantation (HSCT)

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Background

Invasive fungal infections (IFI) are cause of morbidity and mortality in children undergoing hematopoietic stem cell transplantation (HSCT). Prophylaxis with amphotericin B can be limited by renal toxicity; oral triazoles can be inadequate by poor absorption, large inter-individual pharmacokinetic (PK) variability, and hepatotoxicity. Intravenous (i.v.) micafungin (MCF) has potential advantages, because of its better safety profile and lack of drug-drug interactions with common medications used in the HSCT setting. We assumed that higher dose MCF (3-4 mg/kg) three times per week will provide drug exposure similar to standard daily dose (1 mg/kg), improving compliance even in the outpatient setting.

Methods

Fifteen children (M/F 12/3, median age: 11.5 years, range: 2-17) undergoing HSCT received MCF, 3-4 mg/kg i.v. over 1 hour, (every 48-72 hours). Trough plasma (C_0) and peak concentration (C_{max}) were measured at every dosing and a PK profile was defined on day 3. MCF detection was performed by a validated HPLC-MS/MS using a gradient elution (m/z: 1270.2→1172.06).

Results

Measurable plasma concentrations were present in 30/31 samples 48 h after administration, and in 11/15 cases after 72 h. The mean±SD terminal half-life ($t_{1/2}$) was 10.7±2.2 h (range 6.7–14.7) and was comparable to previously published pediatric PK data. On day 3, C_{max} (30’ after the end of the infusion) ranged between 3.5-28.7 mg/L (mean±SD: 13.4±6.8 mg/L). There was no evidence of systemic accumulation after repeated administration. We measured also MCF C_0 on day 7 and it was found 50% compared to day 3 (median 0.36 *vs* 0.71 mg/L). Body weight (BW, kg) influenced MCF systemic exposure (mg*h/L): Dose (mg/kg)/AUC_{0-24} =0.19 * $BW^{-0.55}$, r=0.55). No patient developed IFI and MCF at 3-4 mg/kg was well tolerated. Seven patients experienced increased AST/ALT (four grade 1 and three grade 2 - CTCAE), but no one stopped treatment and mean liver function tests at the end of treatment became normal, indicating the transient nature of these laboratory abnormalities.

Conclusions

These data suggest that alternate day MCF at dosage of 3-4 mg/kg could be a convenient, safe and efficient alternative for antifungal prophylaxis in children at high risk for IFI and merits further prospective evaluation.