Relationship between trough ganciclovir concentration and leukopenia in lung transplant recipients receiving valganciclovir prophylaxis

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Background: Ganciclovir and its prodrug valganciclovir are the first-line agent for cytomegalovirus prophylaxis after lung transplantation. However, administration of these agents is sometimes discontinued due to their associated toxicities, which increase the risk of myelosuppression, including leukopenia. This study primarily aimed to investigate the relationship between trough ganciclovir concentration and hematologic toxicity in lung transplantation patients receiving valganciclovir prophylaxis. The secondary objective was to identify factors affecting ganciclovir pharmacokinetics in this population.

Methods: This prospective observational study included 24 adult lung transplant patients receiving valganciclovir prophylaxis. Follow-up was continued for 3 months after lung transplantation. In total, 57 concentrations of ganciclovir were analyzed (50 points for trough and 7 points for non-trough). The cutoff value of trough ganciclovir concentration in leukopenia grade ≥ 3 (white blood cell < 2,000 /mm^3) was estimated using receiver operating characteristic analysis. Population pharmacokinetic analysis was performed using a nonlinear mixed-effects modeling program.

Results: The trough ganciclovir concentration was significantly higher in the group with leukopenia grades ≥ 3 than in the group with grades ≤ 2 (1605.7 ± 860.1 ng/mL (n = 3) vs 380.5 ± 175.8 ng/mL (n = 21), $p < 0.001$). The cutoff value of trough ganciclovir concentration for ≥ grade 3 leukopenia was estimated as 872.0 ng/mL. Among the three patients with trough ganciclovir concentration ≥ 872.0 ng/mL, all had early cessation of valganciclovir prophylaxis due to leukopenia, and one patient developed cytomegalovirus infection during the observation period. Creatinine clearance and lung re-transplantation were found to have a significant impact on the total body clearance of ganciclovir. Ganciclovir clearance was decreased in patients with reduced creatine clearance or re-transplantation.

Conclusion: These results suggest that higher ganciclovir trough concentrations are associated with an increased risk of leukopenia ≥ grade 3. Therapeutic drug monitoring of valganciclovir may be useful for minimizing drug-related leukopenia in certain population, such as patients with renal dysfunction and lung re-transplantation. These results may help clinicians optimize prophylaxis strategies for cytomegalovirus infection.

Keywords: ganciclovir, valganciclovir, therapeutic drug monitoring, lung transplantation, prophylaxis, cytomegalovirus.