SUMMARY

Extracorporeal elimination of circulating pegylated liposomal doxorubicin to enhance the benefit of cytostatic therapy in ovarian cancer

Background: Encapsulation of cytotoxic drugs into liposomes changes their pharmacokinetic and toxicologic properties in order to enhance the benefit of chemotherapy. Pegylated liposomal doxorubicin (PLD) is one of the most prominent drugs in this group. Despite its reduced cardio- and hematologic toxicity, it confers a higher risk of mucocutaneous toxicity in comparison to its parent drug (*i.e.* doxorubicin, DOX). The specific pharmacokinetic properties of PLD enable its partial elimination from plasma after reaching maximum concentration within the tumor tissue in order to reduce its toxicity.

Aim: This doctoral thesis evaluates the efficacy and safety of plasmafiltration (PF) as a method of extracorporeal PLD elimination, seeking to enhance its therapeutical benefit. The reduction of PLD-related toxicity thanks to the application of PF was determined. Further, PLD pharmacokinetics and the factors affecting it, as well as the effect of PF on the outcome of cancer therapy, were also analyzed.

Material and methods: Sixteen patients with platinum-resistant epithelial ovarian cancer were enrolled in the study. PLD was administered as a one-hour i.v. infusion of 50 mg/m^2 once every four weeks, up to 3–6 cycles. PF was initiated 44–46 h post-infusion. Blood samples were collected at 3, 10, 20, 30, 44 (46), 47 (49), 56, 68, 92, 96, and 116 h after PLD administration. The concentration of PLD and free DOX in plasma was determined through high-performance liquid chromatography with fluorescent detection. A non-linear modeling of mixed effects (controlled = fixed and random effects) was used to create a population pharmacokinetic model for PLD. The PLD fraction eliminated by endogenous mechanisms prior to PF was compared with the fraction removed by PF. The effect of covariates (cycle order, age, body composition, pleural effusion, and pre-cycle white blood cell and monocyte absolute count) on PLD pharmacokinetics was evaluated. PLD-related toxicity was determined using CTCAE v4.0. Treatment response was evaluated using RECIST 1.1 and serum CA 125 evolution.

Results: A total of 53 cycles with PF were evaluated, whereas that four cycles of PLD were administered without performing PF. PF removed 31% (±10%) of the administered PLD dose. Until the start of PF, endogenous clearance (CL_n) was responsible for the elimination of 34% (±7%) of the administered PLD dose. PF enhanced the PLD clearance up to ~42-fold from CL_n baseline values. Free DOX accounted for 10.4% (±4.6%) of total DOX in plasma. No PF-associated DOX leakage from the liposomes was observed. The presence of malignant effusions was associated with increased peripheral volume of distribution in the first and subsequent cycles and with increased CL_n during the first cycle. Other evaluated covariates had no effect on PLD pharmacokinetics. PF was well-tolerated and PF-related adverse events (AEs) were observed in 3 cycles (6%) and technical complications were observed in 4 cycles (7.5%). All of the AEs were mild and resolved spontaneously or with minor intervention. PF was associated with a significant PLD-related toxicity reduction – only one case of grade 3 skin toxicity and one case of grade 1 mucositis were observed. The median progression-free survival (PFS) was 3.6 (1.5–8.1) months, the median overall survival (OS) was 7.5 (1.7–26.7) months. One patient (7%) achieved partial response, 27% patients achieved a stable disease, and 67% patients showed progressive disease.

Conclusion: PF can be considered as a safe and effective method for the extracorporeal removal of PLD, resulting in a lower incidence of mucocutaneous toxicity. The PLD pharmacokinetics observed in this study were consistent with previously published data. The median PFS observed in this study was comparable to historical data, while the median OS and treatment responses were lower. This may be possible to the difference between the study populations, which make a head-to-head survival comparison challenging. Therefore, prospective randomized trials are warranted to evaluate the effect of PF on antitumor therapy efficacy.