Therapeutic drug monitoring (TDM) of Carboplatin (CRB) during tandem high-dose chemotherapy (HDCT) and peripheral-blood stem-cell rescue as salvage treatment of a child with relapsed germ cell tumor (GCT).

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Background. CRB is a widely used antineoplastic agent in childhood cancer, but its use is associated with acute and long-term toxicities. The relationship between drug exposure, quantified by area under the curve (AUC), and efficacy/toxicity is well-established. GCTs, which originate from gonadal or extragonadal cells, are highly sensitive to platinum compounds, and are generally curable, even in the presence of metastasis. However, relapsed or progressive disease are candidates to salvage therapy. The aim of the current study were to measure CRB plasma concentrations and calculate AUCs to ensure adequate medication exposure while minimizing potential adverse effects in a 4 year-old girl with GCT.

Methods. CRB was quantified using a validated high-performance liquid chromatography method coupled to a triple quadrupole mass spectrometer in accordance with regulatory guidelines. Briefly, protein precipitation of plasma samples with methanol containing CRB-d4 was performed, followed by centrifugation and chromatographic separation on a Waters Atlantis® HILIC Silica 3 µm (2.1 × 50 mm) column using a mobile phase gradient of acetonitrile-water (0.1% formic acid and 10 mM ammonium formate) running at a flow rate of 400 µL/min. Detection was performed under positive-electrospray-ion multiple reaction monitoring mode using 372 → 294 and 376→ 298 transitions for CRB and CRB-d4, respectively. Limited sampling at specific time points (before CRB infusion, at the end of CRB infusion and 60, 120, 240, 480, and 720 min post-infusion) facilitated AUC calculation via non-compartmental analysis using Phoenix WinNonlin® (Certara) software.

Results. CRB plasma levels were measured in 61 samples collected over three cycles of CRB treatment, each lasting three days. Nine $AUC_{0\text{-}12h}$ values were calculated to achieve target levels ranging between 18 and 24 min*mg/ml per cycle. AUC values of 16.7, 25.6 and 23.8 min*mg/ml were obtained in each consecutive cycle. The patient's estimated glomerular filtration rates were 158, 179 and 107 ml/min/1,73m2 for each consecutive cycle. Dose adjustments based on AUC results were implemented post-first cycle and throughout subsequent cycles.

Conclusions. Our data demonstrate a feasible and reliable methodology supporting TDM for optimizing CRB dosing in pediatric GCT patients. Notably, the patient did not experience significant renal or auditory toxicity.