Pharmacokinetic and Preliminary Toxicity Investigation of an Innovative Controlled-Release Cisplatin Dry Powder Inhalation Formulation in Sheep

Rémi Rosière,[1,2] R. Bischof,[3] S. Chraibi,[1] P. Gérard,[2] I.Hennia,[2] E. Meeusen,[3] K. Amighi,[1] and N. Wauthoz[1]

[1]Unit of Pharmaceutics and Biopharmaceutics, Université libre de Bruxelles, Belgium; [2]InhaTarget Therapeutics, Belgium; [3]Allergenix Pty Ltd, Australia

remi.rosiere@ulb.be

Background

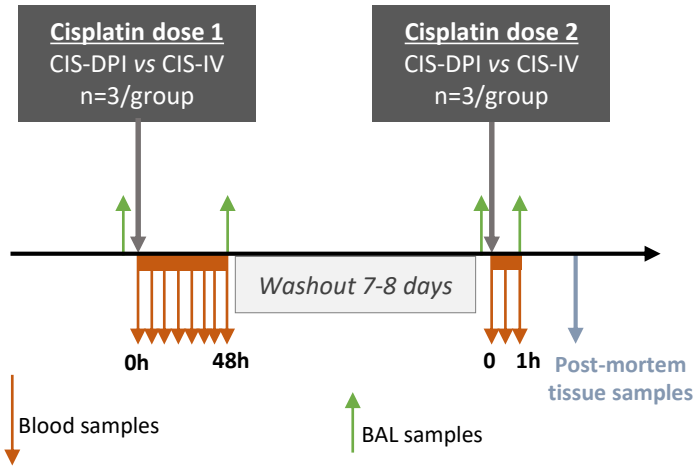
- Cisplatin DPI with controlled-release properties in the lungs to treat lung tumours has lead to promising PK, toxicity and efficacy results in mouse models (Levet et al, Int J Pharm 2017; Levet et al, RDD Europe 2017).
- The sheep respiratory model can be used as a powerful preclinical research tool and for clinical translation of novel therapeutic approaches (Kaminskas et al, Pharm Res 2020).

Aims

In a healthy sheep model:

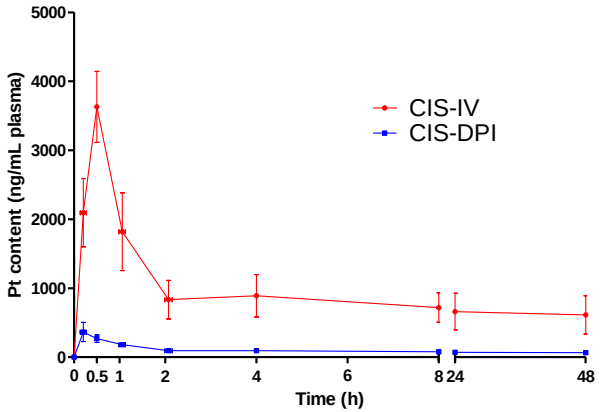
- To compare the PK profile and biodistribution of cisplatin delivered at a dose of **1 mg/kg** as
  - An intravenous perfusion (CIS-IV) , (30-min perfusion)
  - A controlled-release DPI formulation (CIS-DPI), i.e. a spray-dried powder composed of 50% w/w cisplatin, hydrogenated castor oil and vit E TPGS
- Generation of preliminary toxicity data.

Design



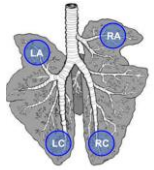
PK Results

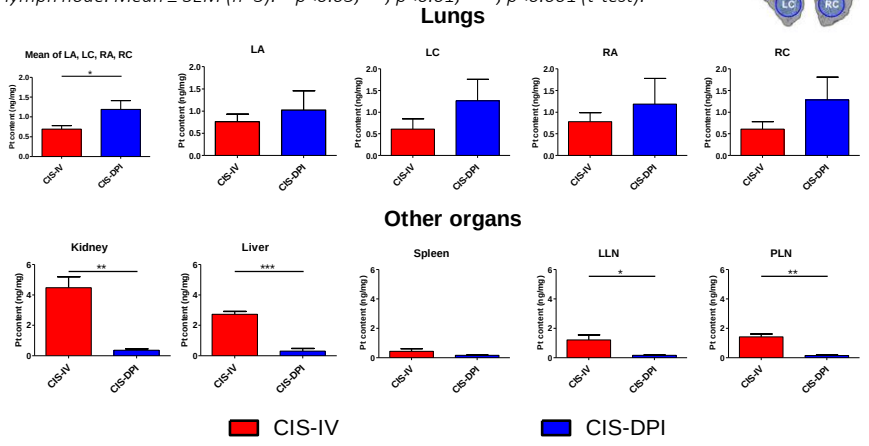
Figure 1. *Platinum PK profiles in plasma following dose 1 of CIS-IV and CIS-DPI. Mean ± SEM (n=3).*



- **Very low systemic exposure to cisplatin with CIS-DPI** compared to CIS-IV (Fig 1), with:
  - → 10-fold reduction in C_{max} (365 ± 138 ng/mL *vs* 3,629 ± 516 ng/mL)
  - → 10-fold reduction in AUC_{0-48} (3,689 **ng.h/mL** *vs* 35,138 ng.h/mL)

Figure 2. *Platinum biodistribution in organs/tissues, 1h following dose 2 of CIS-IV and CIS-DPI. LA=left apical lung lobe, LC=left caudal lung lobe, RA=right apical lung lobe, RC= right caudal lung lobe, LLN= lung-specific lymph node, PLN= popliteal lymph node. Mean ± SEM (n=3). * p<0.05; **, p<0.01; ***, p<0.001 (t-test).*





- **Lung targeting with CIS-DPI** compared to CIS-IV (Fig 2)
  - → significantly 2-fold increased platinum concentration in the lungs (p<0.05, t-test)
  - → significant lower exposure in other organs 1h following administration: e.g. in the kidneys, 0.36 ± 0.08 ng/mg vs 4.5 ± 0.7 ng/mg, respectively (p<0.01, t-test) and in the liver, 0.3 ± 0.2 ng/mg vs 2.7 ± 0.2 ng/mg, respectively (p<0.001)

Preliminary TOX Results

- The general clinical condition was good for all sheep in both groups.
- Non-significant bodyweight loss observed between doses 1 and 2 in both groups (p>0.05, paired t-test), but more pronounced with CIS-IV than CIS-DPI, with ~20% vs ~10% mean loss, respectively.
- All total blood cell counts at the times examined generally lay within the normal range for sheep - RBCs: 9-15 x 10^9/mL; WBCs: 4-12 x 10^6/mL (Shalm's Veterinary Hematology, 2000)
  → *no signs of systemic inflammation nor medullar toxicity observed with CIS-DPI.*
- An increase in leucocyte numbers in BAL was observed after CIS-DPI delivery (Fig 3), indicating possible local airway irritation due to cisplatin.
- **No evidence of any tissue damage or inflammation** within or around the bronchial, alveolar and parenchymal tissues in any of the lung lobes following CIS-DPI administration (Fig 4).

Figure 3. *Total BAL leukocyte numbers before and after CIS-DPI dosing (dose 1 and dose 2, arrows). Mean ± SEM (n=3). * p<0.05 (paired t-test).*

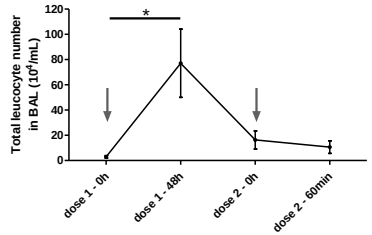
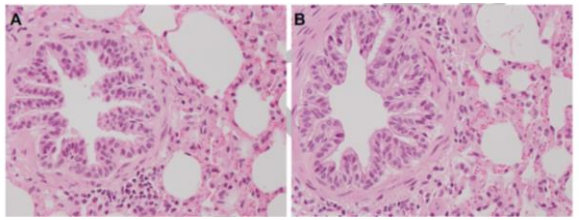


Figure 4. *Lung histology taken from the right caudal lung lobe of (A) control lungs, compared to (B) lungs collected at 1h post-dose 2 CIS-DPI administration (original magnification x400):*



Conclusions and perspectives

- This study confirmed the PK advantage of local cisplatin delivery by means of a controlled-release DPI compared to an IV solution.
- In clinics, the inhaled cisplatin dose is expected to be reduced, which will be in favor of a good general tolerance and acceptance by the lung cancer patients.
- **Clinical translation to the lung cancer patient care is highly anticipated in the upcoming years.**

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