Population Pharmacokinetics and Pharmacodynamics of Cisplatinum During Intraperitoneal Chemohyperthermia Using a Closed Abdominal Procedure

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Introduction

• HIPEC associated with high level of morbidity
• Rare data in literature concerning pk
• Objectives:
  • Study pK and pD of CDDP
  • Using population pharmacokinetic approach
  • Optimize dosage of CDDP
Patients

- Jan 2003-dec 2004 : 40 patients :
  14 with CDDP alone,
  26 CDDP + MMC

- Origin of PC : 16 pseudomyxoma, 13 ovarian origin, 4 mesothelioma, 7 various origin
Methods: surgical procedure

- **Exploration**: PC staging with **Gilly’s classification** and peritoneal cancer index of Sugarbaker (PCI)

- **Complete cytoreduction**

<table>
<thead>
<tr>
<th>Gilly’s Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>Only positive cytology</td>
</tr>
<tr>
<td>Stage 1</td>
<td>&lt; 5 mm, localized</td>
</tr>
<tr>
<td>Stage 2</td>
<td>&lt; 5 mm, diffuse</td>
</tr>
<tr>
<td>Stage 3</td>
<td>5 mm up to 2 cm</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Large malignant cakes</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Peritoneal Cancer Index</th>
<th>Lesion Size</th>
<th>Lesion Size Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Central</td>
<td>LS 1</td>
<td>No tumor seen</td>
</tr>
<tr>
<td>1 Right Upper</td>
<td>LS 2</td>
<td>Tumor up to 5.0 cm</td>
</tr>
<tr>
<td>2 Splenium</td>
<td>LS 3</td>
<td>Tumor &gt; 5.0 cm or confluent</td>
</tr>
<tr>
<td>3 Left Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Left Flank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Left Lower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Pelvis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Right Lower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Right Flank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Upper Jejunum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Lower Jejunum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Upper Ileum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Lower Ileum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td></td>
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</tbody>
</table>
Methods: HIPEC

- **Closed technique** (CAVITHERM®)
- 4-6 litters of perfusate

- 1 to 1.5 mg/kg of CDDP used alone
- 0.8 to 1 mg/kg of CDDP associated with 0.5 to 0.6 mg/kg of MMC

- During **90 min** with inflow temperature between **44 and 46 °C**
Methods: pK and pD studies

• **Pharmacokinetics**:
  - **Blood, perfusate and urine samples**: 1 min, 45 min, 90 min, 3h, 6h, 24h, 48h, 72h, 120h and 240h
  - **NONMEM®** for pharmacokinetics and **X-Pose®** for covariate detection

• **Pharmacodynamics**:
  - **AUC** of CDDP = organism exposure
  - **Toxicity**: renal and haematological complications
  - **Long term effectiveness**: survival and disease free survival
Results: surgery

- Carcinomatosis staging:
  - CC-0 (no residue) = 26 patients (65%)
  - CC-1 (residue < 5mm) = 8 patients
  - CC-2 (residue > 5mm) = 6 patients

- Assessment of completeness cytoreduction:
  - CC-0 (no residue) = 26 patients (65%)
  - CC-1 (residue < 5mm) = 8 patients
  - CC-2 (residue > 5mm) = 6 patients
Results: pharmacokinetics

**Cisplatinum peritoneal concentration**

- CDDP alone (n=14)
- CDDP+MMC (n=26)

Peritoneal resorption = 24h

**Cisplatinum plasmatic concentration**

- CDDP alone (n=14)
- CDDP+MMC (n=26)

Plasmatic resorption > 10 days
Results: pharmacokinetics

→ 2 separated models: population pharmacokinetics

Peritoneal Compartment 1

Peripheral compartment 2

Central compartment Plasma

Peripheral Compartment Plasma

Elimination

Elimination

Elimination

Covariates analysis:

- Weight and PCI: plasmatic clearance
- ALAT: $K_a$

Graphs showing individual predictions and covariates analysis.
Results: pharmacodynamics

<table>
<thead>
<tr>
<th>AUC CDDP</th>
<th>plasmatic</th>
<th>peritoneal</th>
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</thead>
<tbody>
<tr>
<td>mean</td>
<td>97.91</td>
<td>90.87</td>
</tr>
<tr>
<td>sd</td>
<td>90.93</td>
<td>76.55</td>
</tr>
<tr>
<td>median</td>
<td>67.28</td>
<td>68.41</td>
</tr>
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Peritoneal / Plasmatic AUC ratio ≈ 1

- **Haematologic toxicity:**
  - Anemia grade 1 or 2: 75%
  - Leucopenia grade ≤1: 84% (61% grade 0)
  - Thrombopenia grade 1: 34% (55% grade 0)

- **Renal toxicity:**
  - 10 Acute Renal Failure: No correlation with plasmatic or peritoneal AUC
  - Insufficient hydration and digestive preparation

- **Long term Survival**
  - No direct relationship with organism exposure with CDDP
Discussion

• **Plasmatic/Peritoneal AUC** ratio near 1: concept of **peritoneo-plasmatic barrier** for CDDP ??

• **Maximal systemic tolerated dosage of CDDP = maximal HIPEC dosage**

• **Renal** and **haematologic toxicity** are **multifactorial** (surgical and medical complications)

• **Long term survival also multifactorial** (origin of CP, CP stage, …)

difficulty +++ to show a direct relationship with CDDP exposure
Conclusions

- Pharmacokinetic study for HIPEC is possible using 2 bicompartimental models with population pharmacokinetic approach.

- The large number of parameters linked with toxicity or survival make difficult the research of direct interaction between pharmacokinetic and pharmacodynamic.

- Peritoneal surface doesn’t constitute, as supposed, a barrier between peritoneal cavity and plasmatic compartment for CDDP.

- **Cisplatinum HIPEC is equivalent in term of drug exposure as a systemic perfusion.**

- Future works:
  - develop a single model integrating plasmatic and peritoneal compartments
  - integrate volume of abdomen measured with CT scan as a covariate
  - adapt precisely drug dosage with individual parameters to reduce toxicity and optimize effectiveness