Optimal TDM and Pharmacodynamics of Mitotane in Adrenocortical cancer in children and Adults

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Partners working together
Adrenocortical Cancer (ACC)

- relatively uncommon (4-12 per million population), aggressive tumour often detected in advanced stage.
- poor prognosis: 5 yr survival - 15%.
- stages (I-III) – surgical resection.
- ~30-40% stage 4, not curable.
- chemotherapy
  - disappointing outcomes
  - streptozotocin or etoposide/dox/CDDP

1. Fassnacht et al NEJM 2012
Mitotane

- Mitotane (o,p’-DDD)
  - 1,1-(o,p’- dichlorodiphenyl)-2,2-dichloroethane)
  - since 1960.
- orally active - analog of insecticide DDT
- only active systemic therapy for ACC
  - advanced & adjuvant
- drug of choice for unresectable, recurrent and metastatic ACC (+/- chemotherapy).
Mitotane

• partial responses 25-30% of patients, rare CR
• kills adrenal cells
  – mechanism unknown
• reduces hormone production
  – blocks cortisol synthesis by inhibiting cholesterol side chain cleavage and 11 β-hydroxylation
• Substantial toxicity
  • primarily neurological (cerebellar, cerebral) and GI
    – lethargy, somnolence, ataxia, dizziness, vertigo
  • related to high plasma levels
Mitotane Metabolism

• ~40% of dose absorbed
  – 60% → feces
• 10% → urine (water soluble)
• 1-17% excreted via bile
• t1/2 18-159 days

source: BMS product info Lysodren®
Mitotane Metabolism

- Metabolic activation within liver results in formation of 2 metabolites:
  - $\alpha$ hydroxylation $\rightarrow$ DDE
  - $\beta$ hydroxylation $\rightarrow$ DDA (considered active, adrenolytic)

Metabolites

• True effect of metabolites in conjunction with mitotane is currently not known
  • toxicity
  • anti-tumour efficacy

• Measurement of mitotane and metabolites DDA and DDE could provide a better understanding of mitotane PK and PD and guide effective management.
Importance of Plasma Mitotane Measurement

- Mitotane—usual starting dose of 0.5-3 g/d & escalation over several weeks/months
- dose-effect relationship
- Trough concentration in plasma (Cp):
  - Cp <14 mg/L is sub-therapeutic.
  - Cp >20 mg/L is potentially toxic (CNS, BM, GI & renal).
  - Cp 14-20 mg/L is ideal (55-66% objective response rate).
- 5-10 times inter-patient variability of Cp with dose
Cp Mitotane >14 for therapeutic effect

mitotane monotherapy n= 27

Figure 3 Actuarial survival rates from time of diagnosis in 29 patients with evaluable tumour (no operation, n = 5; subtotal operation, n = 24) according to serum levels of mitotane (mitotane therapy given early in the course of their disease). High (H) = serum levels >14 mg l⁻¹; low (L) = serum levels <14 mg l⁻¹. H vs L, P < 0.001.
Therapeutic Drug Monitoring

TDM - warranted to achieve best therapeutic index
  • has been used in European centres
  • recommended for targeting & maintaining Cp 14-20mg/L$^{1,2}$
    • however not routinely used in Australia
  • We are the only centre in the southern hemisphere to provide TDM of mitotane and metabolites$^{3}$.

Previous Data

- 74 patients, >450 levels
  - F/M 44/30, median age 50; 3 children
- starting dose 1-8 g/day (physicians choice)
- 42 patients (24/18 F/M, 3 children) achieved therapeutic range
  - dose required $6.1 \pm 3.2$ (mean ± SD) g/day.
- Time to achieve therapeutic range:
  - adults $5.9 \pm 3.7$ months
  - children $1.5 \pm 0.1$ months.
- Toxic levels (>20 μg/ml):
  - 21 patients(all 3 children)
Mitotane Dose and Plasma Levels

Substantial interpatient variability in mitotane and metabolite levels (mean ± SD)
Patient mitotane and metabolite levels

**a**

Patient 1

- DDA
- Mitotane
- DDE

**b**

Patient 2

- DDA
- Mitotane
- DDE
Patient mitotane and metabolite levels

Master IJ, 13 y
Previous data: Conclusions

- It takes a variable time to achieve therapeutic range
  - 2-6 months
  - some patients overshoot despite TDM.
- substantial inter-patient variability in mitotane & metabolite levels
- role of metabolites in dose adjustment & toxicity unclear
- mitotane and DDE appear to be fat soluble
  - clearance appears slow (weeks)

In a prospective study we aimed to improve time to Cp>14 and to identify factors that account for variability in mitotane kinetics by correlating kinetic parameters with pre-treatment factors.
## Recommended Dose Adjustment According to CNS/GI Side Effects and Plasma Mitotane Levels

<table>
<thead>
<tr>
<th>Plasma Mitotane Level</th>
<th>CNS (Grade 2) / GI (Grade 3/4) Present</th>
<th>CNS (Grade 3/4) Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Increase daily dose by 1 g*</td>
<td>Reduce daily dose by 1 g</td>
</tr>
<tr>
<td>&lt;14 mg/L</td>
<td></td>
<td>Stop mitotane†</td>
</tr>
<tr>
<td>14–20 mg/L</td>
<td>Maintain dose</td>
<td>Reduce daily dose by 1.5 g</td>
</tr>
<tr>
<td>&gt;20 mg/L</td>
<td>Reduce daily dose to 50–75% of the most recent dose</td>
<td>Stop mitotane†</td>
</tr>
</tbody>
</table>

*Up to the maximum tolerated dose; †Until symptom resolution (grade 0 or 1)
Prospective Clinical TDM Study: Aims

- To determine the relationship between mitotane and metabolite levels and toxicity, and confirm the published relationship with response.

- Identify factors accounting for variability in mitotane PK and toxicity.

- Define optimal TDM approach → Cp 14-20 quickly by frequent, informed dose escalation.
Prospective Clinical TDM Study: Plan

- ACC pts multiple institutions
- collect demographic data
- begin mitotane at 1g/day → 2g/day after 1 week
- Cp at 2 weeks
  - <5 → triple dose
  - 5-10 → double dose
  - 10-14 → 1.5x dose
- repeat Cp 4 weeks after dose escalation, then every 2-4 weeks till Cp>14
- Cp >20: stop, rebegin lower dose
Prospective Clinical TDM Study - data so far

- 24 sites across Australia and one in Singapore
- 15 patients to date:
  - F/M 10/5, median age 41 (9-69)
  - 3 children
- starting dose 1-6 g/day, kids 1-4 g/day
- 9 patients (6/3 F/M, 2 children) achieved therapeutic range to date
  - dose required $5.9 \pm 0.3$ (mean $\pm$ SD) g/day
  - adults $5.8 \pm 2.0$ months
  - kids $2.0 \pm 1.6$ months
- Toxic levels ( $>20 \, \mu g/ml$ ) : 5 patients (2 children)
### PK Assessment
(45 yo female, 1\textsuperscript{st} dose)

<table>
<thead>
<tr>
<th>Age</th>
<th>Time (hr)</th>
<th>DDD conc (mg/L)</th>
<th>Mitotane dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41.73</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.44</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>25.08</td>
<td></td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

#### PK Variables

- Half-life (hr): 8.66
- AUC 0-t: 25.80
- Clearance L/hr: 3.88

![AUC (Conc-Time) curve](attachment:image.png)
Conclusions

• more rigorous TDM with specific advice has not changed:
  – time to Cp>14
  – proportion of pts with Cp>20

• Yet to formally assess:
  – conformance with advice
  – toxicity
  – predictive parameters for toxicity/dose-level relationship

• Need to continue study to n= 45-60 (as planned)
Conclusions (2)

- single dose t1/2 is different to repeated dosing
  - likely due to distribution into fat

- role of metabolites?
  - is DDA active (recent data → no)
  - do they affect distribution and effect of mitotane?
Collaborators and Funding

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