Trough dabrafenib plasma concentrations can predict occurrence of adverse events requiring dose reduction in metastatic melanoma

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Introduction

- High variability of response to Kinase Inhibitors (KI)
- Single dose for all patients
- Wide inter-patient pharmacokinetic variability
- Efficacy and safety more related to plasma concentration than to dose
- Increasing evidence for efficacy and toxicity concentration threshold
Concept of threshold

- Efficacy threshold
- Toxicity threshold

Concentration
Notion de seuil

Efficacy threshold

Therapeutic Area

Toxicity threshold

Concentration
Concept of threshold

Imatinib:

Pazopanib:
- 20 mcg/ml in RCC. Suttle B et al. JCO 2010

Vemurafenib:
- 40 mcg/ml in MM. Kramkimel N et al. Target Oncol 2016;11:59-69

Dasatinib:
- 1.5 ng/ml to avoid pleuresia in CML. Rousselot P et al. EHA 2012

Diagram:
- Efficacy threshold
- Toxicity threshold

Nb of patients vs. Concentration
Concept of dose adaptation
Historically, the overall survival was 6-12 months

Frequency and incidence are increasing

Innovative “targeted therapies”

- Through MAP-Kinase pathway (mitogen activated protein kinase)
  - > 20 months improvement of OS (12 months of PFS)
Historically, the overall survival was 6-12 months

Frequency and incidence are increasing

Innovative “targeted therapies”

- Through MAP-Kinase pathway (mitogen activated protein kinase)
  
- > 20 months improvement of OS (12 months of PFS)
Context: metastatic melanoma

- Historically, the overall survival was 6-12 months
- Frequency and incidence are increasing
- Innovative “targeted therapies”

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Frequency and incidence are increasing

Innovative “targeted therapies”

- Through MAP-Kinase pathway (mitogen activated protein kinase)
- > 20 months improvement of OS (12 months of PFS)
Targeted therapy

› Limits:

- Frequent adverse events (90%) : dose adjustments (30%)
- Identical dose to all patients despite interpatient variability of plasma concentration
  - adherence to oral treatment
  - high hepatic metabolism (CYP450)

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Elimination T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib TAFINLAR®</td>
<td>95%</td>
<td>~99.7%</td>
<td>hepatic via CYP3A4 &amp; CYP2C8 2 active metabolites</td>
<td>Biliary: 71 %</td>
<td>8 - 10 h</td>
</tr>
<tr>
<td></td>
<td>97.4%</td>
<td></td>
<td></td>
<td>Urinary: 23 %</td>
<td></td>
</tr>
<tr>
<td>Tramétinib MEKINIST®</td>
<td>72%</td>
<td>97.4%</td>
<td>hepatic via deacetylation (CYP3A4 minor)</td>
<td>Biliary:80%</td>
<td>127h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urinary: 19%</td>
<td></td>
</tr>
<tr>
<td>Vemurafenib ZELBORAF®</td>
<td>Unknown</td>
<td>&gt;99 %</td>
<td>hepatic via CYP3A4</td>
<td>Biliary: (&gt;90 %)</td>
<td>50 h</td>
</tr>
<tr>
<td>Cobimetinib COTELLIC®</td>
<td>46%</td>
<td>95 %</td>
<td>Hepatic via CYP3A4 &amp; UGT2B7 P-gP substrate</td>
<td>Biliary: (&gt;90 %)</td>
<td>43 h</td>
</tr>
</tbody>
</table>
Objective: to determine plasma concentration toxicity thresholds for dabrafenib and trametinib
Method

- Plasma samples were collected from patients with MM treated by dabrafenib ± trametinib in the dermatology department of the Academic Hospital of Bordeaux between March 2016 and March 2017.

- Plasma concentrations were measured at steady-state, at trough concentration (Cmin) before any dose reduction for adverse event.

- Initiated at recommended dose (except in patients > 75 years).

- Collection of clinical data and clinically based dose adjustment.
Method

› Trough dabrafenib and trametinib plasma concentrations were determined using UPLC-MS/MS method

› Plasma threshold of concentration associated with dose reduction for adverse event was studied by ROC-curve analysis
## Results: patients

<table>
<thead>
<tr>
<th>Patients (N)</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>62</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>13/14</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>25.7</td>
</tr>
<tr>
<td>ECOG PS 0-1 (%)</td>
<td>88</td>
</tr>
<tr>
<td>Duration of treatment (median)</td>
<td>3 months</td>
</tr>
<tr>
<td>Patients with adverse events (N)</td>
<td>18</td>
</tr>
<tr>
<td>Patients with adverse events requiring dose reduction (N)</td>
<td>8</td>
</tr>
</tbody>
</table>
Results: plasma concentrations

- A large interindividual variability of trough plasma concentration
  - 15 to 280 ng/ml (CV =104%) for dabrafenib
  - 4 to 24 ng/ml (CV=39%) for trametinib

- Median concentration of dabrafenib: 35 ng/ml

- Median concentration of trametinib: 11 ng/ml

- No differences in dabrafenib plasma concentration between patients who were started at full dose or half dose due to age
Results:

- Median concentration and occurrence of adverse events requiring dose reduction

<table>
<thead>
<tr>
<th>trametinib</th>
<th>dabrafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 ng/ml</td>
<td>&lt;35 ng/ml</td>
</tr>
<tr>
<td></td>
<td>Decrease LVEF</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;11 ng/ml</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Major asthenia</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
</tr>
</tbody>
</table>
## Results

Concentration and dose reduction for adverse event

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients without dose reduction (N=19)</th>
<th>Patients with dose reduction (N=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib mean Cmin (ng/ml)</td>
<td>32 (± 13)</td>
<td>121 (± 84)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Trametinib mean Cmin (ng/ml)</td>
<td>11 (± 4)</td>
<td>13 (± 6)</td>
<td>ns</td>
</tr>
<tr>
<td>Adverse event CTC-AE grade, n</td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>No adverse event</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PFS (month)</td>
<td>5.9</td>
<td>6.9</td>
<td>ns</td>
</tr>
</tbody>
</table>
Results

› Determination of dabrafenib toxicity threshold

Toxicity threshold: 48 ng/ml
Sensibility : 100%
Specificity: 79%
Discussion

- No association between trametinib plasma concentration and adverse events occurrence
- Demonstration of toxicity threshold of 48 ng/ml for dabrafenib
- No difference of PFS between patients with or without dose reduction
- Does dose reduction based on concentration prevent occurrence of AE without loss of efficacy?
Conclusion

- Determination of efficacy threshold is ongoing
- Prospective dose adaptation study is needed
- Therapeutic Drug Monitoring (TDM) may improve safety of dabrafenib
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