PHARMACOKINETICS AND TOXICITY PROFILE OF BENDAMUSTINE IN MYELOMA PATIENTS WITH END-STAGE RENAL DISEASE

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INTRODUCTION
- Bendamustine is a bifunctional alkylating agent with low toxicity that produces both single- and double-strand breaks of DNA, and shows only partial cross-resistance with other alkylating drugs.
- At equieffective doses bendamustine develops more DNA strand breaks than melphalan, BCNU or cyclophosphamide in cisplatin and doxorubicin resistant cell lines of ovarian and breast cancer [1].
- Bendamustine shows a remarkable tumourstatic activity against Hodgkin’s and non-Hodgkin’s lymphomas, multiple myeloma and chronic lymphatic leukaemia [2-5].

Objectives
- Primary objective of this study was to evaluate the plasma kinetics of bendamustine and its main metabolites in cancer patients with renal impairment compared to those with normal kidney function as well as the renal elimination of the drug, and to define dosage recommendations for patients with renal impairment, based on the kinetic and 4-week toxicity profile.

- Secondary objective was to determine the toxicity profile of bendamustine in the maximal 3 subsequent 4-week bendamustine single-agent or combination chemotherapy cycles in all cancer patients enrolled in this study.

METHODS

Study Design
- Phase I, open label, parallel group, multiple dose, multi centre pharmacokinetic and safety study

Subjects
- Men and women (caucasians) 18-75 years of age with advanced malignant tumours were enrolled into the study after having provided written informed consent.
- Group 1: 12 patients (5 m/7 f) with normal kidney status, a mean age of 62.2 years, and a mean body weight of 71.5 kg.
- Group 2: 12 patients (7 m/5 f) with a mean age of 65.5 years, and a mean body weight of 68.4 kg.

RESULTS

Hemodialysis
- Each patient received 120 mg/m2 bendamustine hydrochloride as a 30-min infusion on days 1 and 2 of a 4-week interval. Dialysis-dependent patients were given 120 mg/m2 only on day 1. No further antineoplastic agents were administered during the pharmacokinetic part of the study. Plasma kinetics and urinary excretion were monitored on study day 1.

Safety and Tolerability
- Patients with renal impairment did not experience unusual toxicity ascribable to bendamustine. With the exception of a higher frequency of moderate (CTC grade 2/3) leuko- and thrombocytopenic reactions in patients with renal impairment and end-stage renal disease (CLCreatinine 13.4 – 35.7 mL/min) as well as in investigated three dialysis-dependent patients, about 20 % of the administered dose was recovered as unchanged drug and bendamustine metabolites in urine (Table 2).

Table 2: The average percentage of the dose excreted as parent compound and metabolites in the urine of cancer patients with unimpaired and impaired renal function or eliminated during hemodialysis in dialysis-dependent cancer patients following intravenous administration of 120mg/m² bendamustine hydrochloride to cancer patients with normal and impaired renal function (arithmetic mean/standard deviation)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=12)</th>
<th>Group 2 (n=12)</th>
<th>Total (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLdial (mL/min)</td>
<td>n.a.</td>
<td>15.5/5.5</td>
<td>Total 19.0</td>
</tr>
<tr>
<td>Vz (L)</td>
<td>19.3/14.6</td>
<td>17.0/6.1</td>
<td>19.0/4.3</td>
</tr>
<tr>
<td>t1/2 (min)</td>
<td>29.6/7.2</td>
<td>31.8/10.0</td>
<td>31.3/9.2</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>10780/5702</td>
<td>320/128</td>
<td>1940.4/539.4</td>
</tr>
<tr>
<td>AUC (ng*h/mL)</td>
<td>11657/5068</td>
<td>245/79</td>
<td>4640/1195</td>
</tr>
</tbody>
</table>

Toxicity
- No unusual toxicity ascribable to bendamustine was observed in the patient groups.

CONCLUSIONS
- The results demonstrate that moderate to severe renal insufficiency or failure requiring dialysis did not significantly affect the plasma kinetics of bendamustine and its metabolites following 120 mg/m2 intravenous dose of bendamustine hydrochloride.
- No significant association is evident between renal impairment and both plasma kinetics and toxicity of bendamustine.
- Under conditions of unimpaired liver function a compensatory enhancement of hepatic elimination of bendamustine is conceivable in these renally impaired patients.
- In addition, on the basis of the results it could be expected that a considerable part of bendamustine is eliminated via bile as parent drug and/or metabolites.

- For the chosen administration regime in patients with normal liver function and end-stage renal disease, including dialysis-dependent patients, dose reduction of bendamustine is not necessary.

References

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