Dose-banding of chemotherapy agents and its implications for hematology-oncology practice

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Introduction

Definition of dose-banding

Chemotherapy (CTx) doses are clustered into bands of similar dosage levels within a certain range. The mid-point dose of each band represents the respective prescription dose. This concept allows the preproduction of frequently used doses for CTx substances with adequate stability data.

Advantages

- Reduction of patient waiting time
- Pharmacy workflow optimization
- Standardised production process
- Increased drug/patient safety
- Cost savings

Methods

Establishing the suitability of CTx substances for dose-banding by:

1. Evaluating ordering frequency and prescription practice

Investigations were based on pharmacy-data (Zenyx - database) of all CTx substances used by the Freiburg University Medical Center Hematology and Oncology Department (Med 1) in 2012 and on stability data from the literature. All prescribed CTx doses were banded using the logarithmic method described by Zavery et al. (Fig. 1).

Fig. 1. Logarithmic banding scale

Lower level dose band: mean value of prescription dose and the next lower prescription dose
Upper level dose band: determined from the consecutive lower level of the next dose band up.

2. Analysis of stability

Based on results of the above evaluations a selection of appropriate CTx substances to undertake stability analyses was made. The maximum storage period was set at 3 months.

Physical and chemical stability tests: For this purpose CTx preparations of Gemcitabine, Carboplatin, Bortezomib and 5-FU bolus are made up at the relevant concentrations (within the viable dose bands established). The bags and syringes are incubated at 25°C over the storage period. Quantitative analysis of active ingredient and degradation products are carried out via liquid chromatography at defined storage time points. At all sampling times, a visual inspection of the preparations is carried out for particles and change of colour against a dark and white background. Loss of water is determined by change in weight of the preparations over storage. The pH is measured initially and at the end of the storage time (Table 1).

Microbiological stability tests: In order to simulate the worst case scenario, liquid media are used instead of CTx. All manipulations taking place in the CTx production process are carried out accordingly. The direct inoculation method is employed for evaluation of sterility (Fig. 2). After 3 months storage a container integrity test is performed: media filled sample preparations are inserted into bacteria contaminated broth for 1 hour (Fig. 3). After removal, the preparations are incubated for 14 days and examined for microbiological growth.

Results

1.1 Analysis of CTx prescribing data: Ordering frequency: "Extended top 15 CTxs"

<table>
<thead>
<tr>
<th>Year and CTxs</th>
<th>Total # prescribed</th>
<th>Etoposide</th>
<th>Gemcitabine</th>
<th>Vinorelbine</th>
<th>Oxaliplatin</th>
<th>Carboplatin</th>
<th>5-FU bolus</th>
<th>Paclitaxel</th>
<th>Docetaxel</th>
<th>14 d</th>
<th>Dosebanding (without i.th.)</th>
<th>Total # preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>2031</td>
<td>3230</td>
<td>1382</td>
<td>1954</td>
<td>892</td>
<td>1352</td>
<td>579</td>
<td>1373</td>
<td>1327</td>
<td>5</td>
<td></td>
<td>1503</td>
</tr>
<tr>
<td>2012</td>
<td>2031</td>
<td>3230</td>
<td>1382</td>
<td>1954</td>
<td>892</td>
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<td>579</td>
<td>1373</td>
<td>1327</td>
<td>5</td>
<td></td>
<td>1503</td>
</tr>
</tbody>
</table>

1.3 CTx comparison via dose-banding

2012 data

<table>
<thead>
<tr>
<th>CTx substance</th>
<th># preparations</th>
<th># ¤ dosing-bands ( ¤dosing-bands = 25 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1532</td>
<td>12</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>645</td>
<td>4</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>579</td>
<td>4</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>1373</td>
<td>5</td>
</tr>
<tr>
<td>5-FU bolus</td>
<td>1352</td>
<td>12</td>
</tr>
</tbody>
</table>

1.2 Dose - frequency distribution

Refering to arm A of Fig. 2 (methods section)

Conclusions

For implementing the dose-banding concept, a multidisciplinary approach is crucial. Moreover, the careful selection of suitable CTx agents is a key element of introducing dose-banding. Advantages, such as workflow optimization for pharmacy departments and reduction of in- and outpatient waiting time, without compromising patient safety, are convincing arguments for dose-banding.

References

1. ESCMID European Pharmacoepidemiology, 8th Edition, Chapter 2.6.1, Sterility
5. Pharmacy Department Addenbrookes Hospital, Cambridge, UK, personal communication, 2013/14