Dose-banding of cytostatic drugs

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David Devolder PharmD
apo.oncologie@uzleuven.be
Overview

• General aspects
• Dose-banding as a concept
• Perspectives

• Pilot project at UZ Leuven
• Key points
Approach to prescribing chemotherapy

• Traditional calculation based on BSA*
  – Body weight and height
  – Different formulas
  – Estimation versus measurement
  – Obesity and cachexia?

* except Carboplatin (AUC, creat), Thiotepa (mg/kg)
Which formula to choose?

Note: Variance between formulae is greatest for short ‘stocky’ individuals (-9.59% to +5.94%) but in practice BSA may be capped at 2.2 unless the body weight is muscle. Variance may approach 5% in tall thin individuals. This inherent variance is hidden by rounding BSA to one decimal place.

Figures adopted from Gillian, A. (2008), UTD (accessed 2/7/2015)
## Potential sources of variability in chemotherapy dosing

<table>
<thead>
<tr>
<th>Factor</th>
<th>Potential variation</th>
<th>Examples of potential sources of variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient weight, height, BSA</td>
<td>±10%</td>
<td>Shoes, clothing, time of day, calibration, method of BSA calculation</td>
</tr>
<tr>
<td>PK/PD</td>
<td>±15%</td>
<td>Pharmacogenetics, disease effects, hepatic or renal dysfunction, comorbidities</td>
</tr>
<tr>
<td>Vial contents</td>
<td>±15%</td>
<td>Manufacturer, vial type, aseptic technique</td>
</tr>
<tr>
<td>Syringe/infusion bag accuracy</td>
<td>±5%</td>
<td>Manufacturer, type, size, user</td>
</tr>
<tr>
<td>Residual volume during administration</td>
<td>±5%</td>
<td>Filter adsorption, administration set, inadequate flushing of line</td>
</tr>
</tbody>
</table>

*Table adapted from Zavery & Marsh (2011)*
Must patients be given exactly the prescribed dose?

- Is prescribed dose:
  - Scientifically based: controversy on individualised dosing algorithms?
  - Clinically important: impact on outcome of tailor-made versus standard strength?
- Can pharmacy prepare exactly the prescribed dose?
- Is the exact dose ever administrated to patients?

Figure adopted from Mathijssen et al. (2007)
Dose-banding: what’s in a name?

A system whereby

- Through agreement between prescribers and pharmacists,
- Doses of intravenous cytostatic drugs calculated on an individualized basis (from BSA or other criteria), are grouped into defined ranges or bands,
- Doses are rounded up or down to predetermined standard doses,
- The maximum variation of the adjustment between the standard dose and the doses constituting each band is (usually) 6% or less.


≠ Dose-rounding!

Figure adopted from Bins, S. et al. (2014)
A step towards standardisation

- Cytostatic drugs are high risk medication
- Standardisation as a mean to reduce the risk for possible errors during:
  - Prescribing
  - Preparation
  - Administration
- Pragmatic approach to standardise where we can, to provide medication on time and use freed-up time to focus on difficult and individualised therapies
- Already common for targeted therapies
Methods of dosing

- (Flat/fixed dosing: -Mabs/oral chemotherapy)
- Linear model
  - BSA based
  - Target dose based
- Logarithmic model
  - Modified
Linear dose-banding

- BSA based dose-banding
  - Band = BSA-interval (increments of BSA, e.g. [1.45-1.54m²]; [1.55-1.64m²],…)
  - Patient’s BSA is rounded up or down to one decimal place and a set dose band given for that BSA (e.g. 1.5m²; 1.6m²,…)
  - e.g. Doxorubicin 50mg/m²
    - BSA 1.73m² = 1.7m² → band dose = 85mg (1.8% deviation)

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>BSA Range</th>
<th>50</th>
<th>50</th>
<th>60</th>
<th>60</th>
<th>75</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4</td>
<td>1.40-1.44</td>
<td>70</td>
<td>-2.7</td>
<td>85</td>
<td>-1.6</td>
<td>110</td>
<td>+4.8</td>
</tr>
<tr>
<td>1.5</td>
<td>1.45-1.54</td>
<td>75</td>
<td>+3.4</td>
<td>90</td>
<td>+3.4</td>
<td>110</td>
<td>-4.8</td>
</tr>
<tr>
<td>1.6</td>
<td>1.55-1.64</td>
<td>80</td>
<td>+3.2</td>
<td>95</td>
<td>-3.5</td>
<td>120</td>
<td>+3.2</td>
</tr>
<tr>
<td>1.7</td>
<td>1.65-1.74</td>
<td>85</td>
<td>+3.0</td>
<td>100</td>
<td>-4.2</td>
<td>130</td>
<td>+5.1</td>
</tr>
<tr>
<td>1.8</td>
<td>1.75-1.84</td>
<td>90</td>
<td>+2.9</td>
<td>110</td>
<td>+4.8</td>
<td>135</td>
<td>+2.9</td>
</tr>
<tr>
<td>1.9</td>
<td>1.85-1.94</td>
<td>95</td>
<td>+2.7</td>
<td>115</td>
<td>+3.6</td>
<td>140</td>
<td>-3.8</td>
</tr>
<tr>
<td>2.0</td>
<td>1.95-2.04</td>
<td>100</td>
<td>+2.6</td>
<td>120</td>
<td>+2.6</td>
<td>150</td>
<td>+2.6</td>
</tr>
<tr>
<td>2.1</td>
<td>2.05-2.14</td>
<td>105</td>
<td>+2.4</td>
<td>125</td>
<td>-2.6</td>
<td>160</td>
<td>+4.1</td>
</tr>
<tr>
<td>2.2</td>
<td>2.15-2.2</td>
<td>110</td>
<td>+2.3</td>
<td>130</td>
<td>+0.7</td>
<td>165</td>
<td>+2.3</td>
</tr>
</tbody>
</table>
Linear dose-banding

- **Target dose based banding**
  - Band = **dose-interval**
  - Individual dose is rounded up or down to the nearest target dose
  - e.g. Doxorubicin 50mg/m²
    - BSA 1.73m² = 86.5mg
    - Bandwidth = [82.6-87.5]
    - → target dose = 85mg (1.8% deviation)

<table>
<thead>
<tr>
<th>CHOP (50mg/m²) Surface area (m²)</th>
<th>Dose range (mg)</th>
<th>Banded dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27.6 - 32.5</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>32.6 - 37.5</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>37.6 - 42.5</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>42.6 - 47.5</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>47.6 - 52.5</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>52.6 - 57.5</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>57.6 - 62.5</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>62.6 - 67.5</td>
<td>65</td>
</tr>
<tr>
<td>1.35 – 1.45</td>
<td>67.6 - 72.5</td>
<td>70</td>
</tr>
<tr>
<td>1.46 - 1.54</td>
<td>72.6 - 77.5</td>
<td>75</td>
</tr>
<tr>
<td>1.55 – 1.64</td>
<td>77.6 - 82.5</td>
<td>80</td>
</tr>
<tr>
<td>1.65 – 1.74</td>
<td>82.6 - 87.5</td>
<td>85</td>
</tr>
<tr>
<td>1.75 – 1.84</td>
<td>87.6 - 92.5</td>
<td>90</td>
</tr>
<tr>
<td>1.85 – 1.94</td>
<td>92.6 - 97.5</td>
<td>95</td>
</tr>
<tr>
<td>1.95 – 2.05</td>
<td>97.6 - 102.5</td>
<td>100</td>
</tr>
<tr>
<td>2.06 – 2.15</td>
<td>102.6 - 107.5</td>
<td>105</td>
</tr>
<tr>
<td>2.16 – 2.3</td>
<td>107.6 - 115</td>
<td>110</td>
</tr>
</tbody>
</table>
Linear dose-banding

Inconsistent relationship between bands

- Impact on dose ranges
- Impact on dose modifications
- Impact on margin of error

"It sort of makes you stop and think, doesn’t it.”
Logarithmic dose-bandimg

- **Starting or pivot point** = 100mg
  - 25% increase between one dose and two higher, or 11.8% between 2 doses
  - 20% decrease between one dose and two lower, or 10.6% between 2 doses
  - Dose interval = e.g. [94.6-105.7]
    - band dose = 100mg
    - 25% dose escalation = 125mg
    - 20% dose reduction = 80mg

*Figure adapted from Hall, G. (2012)*
Merits of a logarithmic scale

• Consistent relationship between doses
  – Margin of error progresses equally
  – Maximum error 6% or less
  – Better dose rationalisation?
  – IT-friendly
  – Single sequence covers all doses (1mg-100,000mg range)
  – (Standardisation between cancer centres)
**Modified logarithmic dose-banding**

- Volume is taken into account
  - Small adaptation with minimal impact on deviation
  - e.g. Regimen Paclitaxel 175mg/m² - 6mg/ml
    - BSA 1.73m² → 302.75mg
    - LDB = 305.2mg (+0.8%) → 50.9ml
    - 50.9ml is rounded to the nearest 1ml volume → 51ml or dose to be given 306mg (+1.06%)

<table>
<thead>
<tr>
<th>Lower</th>
<th>Upper</th>
<th>LDB dose</th>
<th>mLDB dose</th>
<th>LDB volume</th>
<th>mLDB volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>132.17</td>
<td>147.77</td>
<td>139.8</td>
<td>141.0</td>
<td>23.3</td>
<td>23.5</td>
</tr>
<tr>
<td>147.77</td>
<td>165.21</td>
<td>156.3</td>
<td>156.0</td>
<td>26.0</td>
<td>26.0</td>
</tr>
<tr>
<td>165.21</td>
<td>184.72</td>
<td>174.7</td>
<td>174.0</td>
<td>29.1</td>
<td>29.0</td>
</tr>
<tr>
<td>184.72</td>
<td>206.52</td>
<td>195.3</td>
<td>195.0</td>
<td>32.6</td>
<td>32.5</td>
</tr>
<tr>
<td>206.52</td>
<td>230.89</td>
<td>218.4</td>
<td>219.0</td>
<td>36.4</td>
<td>36.5</td>
</tr>
<tr>
<td>230.89</td>
<td>258.15</td>
<td>244.1</td>
<td>243.0</td>
<td>40.7</td>
<td>40.5</td>
</tr>
<tr>
<td>258.15</td>
<td>288.62</td>
<td>273.0</td>
<td>273.0</td>
<td>45.5</td>
<td>45.5</td>
</tr>
<tr>
<td>288.62</td>
<td>322.68</td>
<td>305.2</td>
<td>306.0</td>
<td>50.9</td>
<td>51.0</td>
</tr>
</tbody>
</table>
Impact of dose-banding

**Pre dose-banding**

**Post dose-banding**

Paclitaxel

- 99 different doses: 6 to 552 mg
- 28 different doses (vs 99)
- 7 doses = 85% of all given
Perspective on all levels

☑️ Advantage

• Treatment delays reduced/eliminated
• Control of workload
• Prepare in advance – ready to use
• Drug wastage minimised/eliminated – reduced costs
• Standardisation *(Nexuz health)*
• Prospective QC and end-product testing
Perspective on all levels

✔️ Advantage
• Treatment delays reduced/eliminated
• Prepare in advance – ready to use
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• Standardisation (Nexuz health)
• Control of workload
• Prospective QC and end-product testing

❌ Disadvantage
• Not applicable for all molecules
• Not supported by all clinical trials
• (Impact on patients outcome?)
• Management
Management

- From ex tempore preparation towards batch production
  - Assurance of quality, safety, efficacy
  - Physicochemical stability studies and international literature analysis
  - Prospective QC:
    - Environmental monitoring of production area (e.g. temperature, pressure, particles, microbial)
    - Validation of equipment (e.g. automated processes, robots), facilities and processes
    - Qualification of operators (e.g. education, media fill, finger prints,…)
    - Extensive quality control procedures: SOPs, batch control and batch assessment, storage monitoring,…
  - End-product testing *(nice to have)*:
    - Analysis for drug identification and drug content *(pharmacopoeia standards)*
    - Sterility testing
    - Practical implications: software, automatization (e.g. prescription, preparation), labelling, storage capacity, distribution,…
    - …
Cytotoxic drugs amenable to dose-banding

• Agents:
  – 5-Fluorouracil, Cyclophosphamide, Epirubicin, Doxorubicin, Gemcitabine, Oxaliplatin, Carboplatin, Docetaxel, Paclitaxel, Irinotecan, (-Mabs, Leucovorin,…), …

• Key factors to keep in mind:
  – Cost (€)
  – Shelf-life
  – Stability (physicochemical, microbial)
  – Prescribing frequency (e.g. FOLFIRI, De Gramont)
  – Management
UZ Leuven

- Annually 15,000 Mabs made on wards
- Annually 60,000 cytotoxic preparations by CPU (Cytotoxic drug Preparation Unit)
  - Daily average production of 230 preparations
  - 60% intended for day clinics
  - Peak time between 10am-2pm
  - Mean lead time 1 hour

- Chemotherapy activities expected to increase with the anticipated burden of cancer
Cytostatic drug preparation unit

- 5 oncology pharmacists
- 6 pharmacy technicians + 2 pharmacists
- E-prescribing of chemotherapy (CPOE, KWS)
  - Order list
  - Exceptions (e.g. ICU transplant, dermatology, ophthalmology)
- 5 Biohazard Safety Cabinets
  - 3 BSC permanent in use
  - 1 BSC installed with Diana pump for preparation of 5-Fluouracil (infusion bags and elastomeric pumps) and stock solutions (e.g. Endoxan)
  - 1 spare BSC (occupied during peak time)
Future

• Building a new high standard (aseptic) drug preparation facility
  – Cleanrooms
  – Isolators

• Quality systems
  – Scanning
  – Tracking system (time slots?)
  – In process control (e.g. CATO, IV Soft)

→ Contributes to a potential higher lead time
→ Pro active decision to implement dose-banding
Project timeline

- Autumn 2014
  - Literature review
  - Presentation for pharmacy staff
- Spring 2015
  - Retrospective data analysis of prescribed chemotherapy during 2012-2014
  - Setting up a modified logarithmic algorithm for 5-Fluorouracil, Gemcitabine, Cisplatin, Oxaliplatin and Irinotecan
  - Presentations for pharmacy department, IT department, oncology board (LKI), nursing staff, and hospital management
- Autumn 2015
  - Final approval from LKI
  - Pilot digestive oncology department
- Spring 2016
  - Getting priority from IT
  - First results expected in spring 2016?
Flow

• Dose-bandung defined in background of E-prescription
• If standard dose is available, system will suggest standard dose (% deviation will be shown)
• Overrule by clinicians remain possible, but must be motivated (clinical freedom)
• Not > 6% deviation between individual calculated dose and standard dose
Practical: UZ Leuven example

Regimen “cisplatin 50mg/m² levofolinic acid 200mg/m² IV fluorouracil 400mg/m² IV + 2400mg/m²/46u infusor q2w”

-BSA: 1,81 m²
-Calculated dose: 4344mg
-Interval: [3939;4403]
-Standard dose: 4175mg
-Variation: 3,9% < 6%

Pivot point = 400mg
Practical: UZ Leuven example

- Aantal unieke doseringen (n) = 91
- 1386 bereidingen in 2014
- Aantal standaarddoseringen = 10, waarvan 4 in voorraad kunnen genomen worden (= 87%)
Expectations

- Process optimization
  - Shorter lead time (< 1 hour)
  - Increase preparations on d-X
    - Batch production – ready to use
    - Better capacity planning
  - Reduction patient waiting time
    - Increasing throughput at day clinic
    - e.g. Oxaliplatin and modified De Gramont 5-FU

Regimen time ± 3 hours
Key points

• Teamwork and effective communication
  – Support needed from oncologists and nursing staff
    • Informative and well constructed proposal
    • Determine the clinical acceptable deviation (e.g. not > 6%)
    • Guarantee clinical freedom
  – Raise awareness of drug-use process after E-prescribing

• Dynamic process
  – Periodical evaluation of clinical trends
There is *compelling rationale* for dose-banding, so take the opportunity!

Thank you for your attention
Literature

- CHATELUT, E. et al. (2012). Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents. British Journal of Cancer, 107, 1100-1106
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