Basic Calculation in Oncology
What and Why?

Foo Koon Mian
Pharmacy Resident
National University of Singapore
Hematology / Oncology Pharmacy Residency Program

4th APOPC 2012
1-3 November 2012
Outline

- Use of BSA in chemotherapy dosing
- Chemotherapy dosing in obesity
- Chemotherapy dosing in amputees
- Estimation of renal function
- Carboplatin dosing using Calvert formula
- Take home messages
Body Surface Area Formulae

- **DuBois & DuBois (1916)**
  \[
  \text{BSA} = 0.20247 \times \text{Ht (m)}^{0.725} \times \text{Wt (kg)}^{0.425}
  \]

- **Boyd (1935)**
  \[
  \text{BSA} = 0.0003207 \times \text{Ht (cm)}^{0.3} \times \text{Wt (g)}^{0.7285 - (0.0188 \times \log(\text{wt}))}
  \]

- **Gehan & George (1970)**
  \[
  \text{BSA} = 0.0235 \times \text{Ht (cm)}^{0.42246} \times \text{Wt (kg)}^{0.51456}
  \]

- **Haycock et al. (1978)**
  \[
  \text{BSA} = 0.024265 \times \text{Ht (cm)}^{0.3964} \times \text{Wt (kg)}^{0.5378}
  \]

- **Mosteller (1987)**
  \[
  \text{BSA} = \sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3600}}
  \]
Body Surface Area - History

- Pinkel (1958)
  - Retrospective analysis of therapeutic dose per unit weight vs per unit BSA for 5 drugs
    - Mechlorethamine, methotrexate, 6-mercaptopurine, actinomycin D, and triethylenethiophosphoramide
  - Similarity of the dosage per unit of BSA among animals and man
  - Recommended BSA to be used for chemotherapy dosing

- Became the standard of dosing for chemotherapy till now

Body Surface Area – not perfect

- However, there were no pharmacokinetic or efficacy studies then to confirm Pinkel’s findings.

- Interpatient variability, in terms of pharmacokinetic parameters, still exist.
  - Physiological factors
  - Intrinsic factors
  - Environmental factors
Body Surface Area – not perfect

- Therefore, since 1990s, several studies are conducted to look for correlation between pharmacokinetic of anticancer drugs and BSA of patient
  - Clearance of several chemotherapy drugs were shown to be not correlated to BSA
  - Eg. etoposide, ifosfamide, epirubicin, 5FU

Felici et. al. Euro J Cancer ;2002; 38;1677–84
Alternative Dosing Methods

- Few other dosing methods have been proposed for chemotherapy dosing
  - Renal function
  - Enzyme phenotyping (CYP 3A4)
  - Pharmacogenetic
  - Flat-fixed doses

Felici et. al. Euro J Cancer ;2002; 38;1677–84
Mathijssen et. al. The Oncologist 2007;12:913–23
Which BSA Formula?

- Which formula should we use?
  - ASCO recommends any of the formula
  - No evidence supporting one formula over another

- Mosteller Formula is most commonly used
  - Easy to use
  - Easy to remember

Outline

• Use of body surface area (BSA) in dosing
• Dosing in obesity
• Dosing in amputees
• Estimation of renal function
• Carboplatin dosing using Calvert formula
• Take home messages
Dose Modification in Obesity

- Overweight (body mass index, BMI > 25 kg/m²)
- Obesity (BMI > 30 kg/m²)
- Common practice of doing large dose reductions at 1st cycle for obese patients
  - Fear of excessive toxicity
- Doses rarely escalated in subsequent cycles
- Are we underdosing our patients?
Different Approaches for Dosing in Obesity

- Various non-evidenced based approaches
  - Actual body weight
  - Ideal body weight (IBW)
  - Adjusted ideal body weight (between actual weight and IBW)
  - Capping BSA @ eg. 2 m²
Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

ASCO Guidelines – Obesity (1)

- Use of actual body weight for dosing chemotherapy
  - Crucial when treatment goal is to cure
    - No evidence of increased short- or long-term toxicity
  - Myelosuppression is the same or less in obese patients with cancer than in non-obese patients
  - Reduced doses may result in poorer disease-free and overall survival rates

# Evidences For Actual Body Weight Dosing

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>STUDY DESIGN</th>
<th>PATIENT GROUP</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgiadis MS et. al. J Natl Cancer Ins 1995; 87:361-6</td>
<td>Retrospective analysis</td>
<td>262 small-cell lung cancer patient receiving chemotherapy</td>
<td>Obesity not associated with toxicities</td>
</tr>
</tbody>
</table>
| Rosner GL et. al. J Clin Oncol 1996; 14:3000-8 (Cancer and leukemia group B study 8541) | Retrospective analysis   | 1,435 Breast cancer women receiving adjuvant cyclophosphamide, doxorubicin, and fluorouracil | - No significant difference in grade 3 toxicity  
- Obese patients who received $< 95\%$ of the full dose had worse failure-free survival rates |
## Evidences For Actual Body Weight Dosing

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>STUDY DESIGN</th>
<th>PATIENT GROUP</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poikonen P et. al. Acta Oncol 2001; 40:67-71</td>
<td>Retrospective review</td>
<td>340 breast cancer women treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil</td>
<td>Leukocyte nadirs were less pronounced among obese patients</td>
</tr>
<tr>
<td>Schwartz J et. al. Gynecol Oncol 2009; 114:53-6</td>
<td>Retrospective review</td>
<td>59 women with endometrial or ovarian cancer with a Body surface area (BSA) &gt;2 m²</td>
<td>No excess toxicity in comparison doses capped at a maximum BSA</td>
</tr>
</tbody>
</table>
ASCO Guidelines – Obesity (3)

- Evidence base for this guideline is different from that of other ASCO guidelines

- There are no prospective randomized studies comparing full weight-based vs non-full weight-based dose selection for chemotherapy

- Mainly based on retrospective analyses of randomized trials and comparative observational studies

Outline

• Use of body surface area (BSA) in dosing
• Dosing in obesity
• Dosing in amputees
• Estimation of renal function
• Carboplatin dosing using Calvert formula
• Take home messages
Amputees – PK alteration

- Drug distribution
  - Change in body composition
  - ↓ Size of vascular system
  - Cardiac output may change

- Drug metabolism
  - Unlikely to change

- Drug excretion
  - Unlikely to change
Various Approaches for Dosing in Amputees

- BSA dosing using pre-amputation height and weight
- Dose modification based on weight reduction
Dose Modification Based On Weight Reduction

Subtract noted percent of body weight for amputees.
Various Approaches for Dosing in Amputees

- BSA dosing using pre-amputation height and weight
- Dose modification based on weight reduction
- Dose modification based on BSA reduction
Dose Modification Based On BSA Reduction

<table>
<thead>
<tr>
<th>Body Part</th>
<th>% Surface Area of Amputated Part</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand and five fingers</td>
<td>3.0</td>
</tr>
<tr>
<td>Lower part of arm</td>
<td>4.0</td>
</tr>
<tr>
<td>Upper part of arm</td>
<td>6.0</td>
</tr>
<tr>
<td>Foot</td>
<td>3.0</td>
</tr>
<tr>
<td>Lower part of leg</td>
<td>6.0</td>
</tr>
<tr>
<td>Thigh</td>
<td>12.0</td>
</tr>
</tbody>
</table>

$$BSA (m^2) = BSA - \left[(BSA) \times (\%BSA_{part})\right]$$, where BSA = body surface area, $$BSA_{part} =$$ body surface area of amputated part.

Dosing in Amputees

- No evidence of which approach is better
- No established guidelines regarding dosing in amputees
- Need for trials and standardisation
- Theoretically, taking into account that metabolism and excretion of drugs are unlikely to change
  - Dosing using pre-amputation height and weight is not unreasonable
Outline

• Use of body surface area (BSA) in dosing
• Dosing in obesity
• Dosing in amputees
• Estimation of renal function
• Carboplatin dosing using Calvert formula
• Take home messages
Renal Function - GFR

- Important information prior to starting chemotherapy
- Glomerular filtration rate (GFR) is generally used as an index of renal function
- $^{51}$Cr-EDTA method is widely accepted as the ‘gold standard’ in determining GFR
- Costly, invasive and is not available in many countries

Estimation of Renal Function

- More convenient methods of GFR estimation have been proposed

- Creatinine clearance
  - 24-hour collection of urinary creatinine
  - Time consuming and labor intensive

- Serum creatinine
  - Several formulae
Examples of Formulae to calculate estimated GFR

- **Cockcroft and Gault**
  \[
  \frac{(140 - \text{age}) \times \text{wt} \times [1 - (0.15 \times \text{sex})]}{(0.814 \times \text{Scr})}
  \]

- **Jelliffe**
  \[
  \frac{[98 - 0.8 \times (\text{age} - 20)] \times [1 - (0.01 \times \text{sex})] \times (\text{BSA}/1.73)}{(\text{Scr} \times 0.0113)}
  \]

- **Wright**
  \[
  \frac{[6580 - (38.8 \times \text{age})] \times \text{BSA} \times [1 - (0.168 \times \text{sex})]}{\text{Scr}}
  \]

- **MDRD**
  \[
  3277 \times (\text{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \times \text{sex})
  \]

Sex: Male = 0, Female = 1
Estimation of Renal Function using Serum Creatinine

- **Advantages**
  - Convenient to obtain serum creatinine level
  - Inexpensive lab test

- **Disadvantages**
  - Accuracy and precision are affected by several factors
    - Age, muscle mass, diet, and proximal tubule secretion of creatinine
    - Inaccurate estimation in amputees

### Comparing Different GFR Formula

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>GFR formula producing least bias and most precise estimates</th>
<th>GFR formula producing most bias and least precise estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>Jelliffe</td>
<td>Wright</td>
</tr>
<tr>
<td>50–100</td>
<td>MDRD/Cockcroft–Gault</td>
<td>Jelliffe/Wright</td>
</tr>
<tr>
<td>&gt;100</td>
<td>Cockcroft–Gault</td>
<td>MDRD/Jelliffe</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Jelliffe</td>
<td>Wright</td>
</tr>
<tr>
<td>40 to &lt; 70</td>
<td>Cockcroft–Gault</td>
<td>Jelliffe</td>
</tr>
<tr>
<td>70 +</td>
<td>Wright</td>
<td>Jelliffe</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>Cockcroft–Gault</td>
<td>Wright/MDRD</td>
</tr>
<tr>
<td>18.5 to &lt; 25</td>
<td>MDRD/Cockcroft–Gault</td>
<td>Wright</td>
</tr>
<tr>
<td>25 to &lt; 30</td>
<td>Cockcroft–Gault</td>
<td>MDRD/Jelliffe</td>
</tr>
<tr>
<td>30 +</td>
<td>Wright</td>
<td>MDRD/Jelliffe</td>
</tr>
</tbody>
</table>

Ainsworth et. al. Annals of Oncology 2012;23: 1845–53
Estimation of Renal Function in Obese patients?

- How should we estimate creatinine clearance in obese patients?
- Which weight should we use?
  - Actual body weight?
  - Ideal body weight?
  - Adjusted ideal body weight?
Examples of Formulae to calculate estimated GFR

- **Cockcroft and Gault**
  \[(140 – \text{age}) \times \text{wt} \times [1 – (0.15 \times \text{sex})]\]
  \[(0.814 \times \text{SCr})\]

- **Jelliffe**
  \[[98 – 0.8 \times (\text{age} – 20)] \times [1 – (0.01 \times \text{sex})] \times (\text{BSA}/1.73)\]
  \[(\text{SCr} \times 0.0113)\]

- **Wright**
  \[[6580 – (38.8 \times \text{age})] \times \text{BSA} \times [1 – (0.168 \times \text{sex})]\]
  \[\text{SCr}\]

- **MDRD**
  \[3277 \times (\text{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \times \text{sex})\]

Sex: Male= 0, Female= 1
Estimation of Renal Function in Obese patients?

For the patients weighing ≥30% over their IBW

<table>
<thead>
<tr>
<th>GFR formula</th>
<th>Degree Of Bias</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cockcroft–Gault</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABW</td>
<td>11.5 (−2.8 to 26.3)</td>
<td>15.9 (6.4–27.2)</td>
</tr>
<tr>
<td>IBW</td>
<td>−26.3 (−36.4 to −16.0)</td>
<td>26.7 (17.8–36.7)</td>
</tr>
<tr>
<td>IBW + 30%</td>
<td>−4.2 (−17.3 to 9.2)</td>
<td>12.6 (6.0–25.8)</td>
</tr>
<tr>
<td><strong>Jelliffe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABW</td>
<td>−10.7 (−24.1 to 2.1)</td>
<td>18.0 (8.4–28.8)</td>
</tr>
<tr>
<td>IBW</td>
<td>−25.9 (−36.9 to −14.4)</td>
<td>26.0 (17.6–37.0)</td>
</tr>
<tr>
<td>IBW + 30%</td>
<td>−17.2 (−29.4 to −4.3)</td>
<td>20.1 (11.6–30.4)</td>
</tr>
<tr>
<td><strong>Wright</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABW</td>
<td>4.0 (−10.2 to 19.2)</td>
<td>13.2 (6.3–24.7)</td>
</tr>
<tr>
<td>IBW</td>
<td>−12.9 (−23.8 to 1.8)</td>
<td>17.3 (10.4–26.8)</td>
</tr>
<tr>
<td>IBW + 30%</td>
<td>−2.6 (−14.9 to 13.9)</td>
<td>14.4 (6.6–24.4)</td>
</tr>
<tr>
<td>MDRD</td>
<td>−15.7 (−32.0 to 2.7)</td>
<td>22.2 (9.8–33.4)</td>
</tr>
</tbody>
</table>

Ainsworth et. al. Annals of Oncology 2012;23: 1845–53
Outline

- Use of body surface area (BSA) in dosing
- Dosing in obesity
- Dosing in amputees
- Estimation of renal function
- Carboplatin dosing using Calvert formula
- Take home messages
Carboplatin

- Cleared 70% by glomerular filtration
- Carboplatin plasma clearance is linearly related to GFR
- Clearance of Carboplatin correlates better with AUC than with BSA

Calvert et al J Clin Oncol 1989;7:1748-56
Carboplatin Dosing

- Formula based on renal function is derived
  \[ \text{Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25) \]

- AUC correlates with thrombocytopenic nadir
  - AUC of 4-6 for 3 weekly regime gave rise to manageable hematological toxicity
  - AUC of 2 for weekly regime

Calvert et al J Clin Oncol 1989;7:1748-56
GFR for Carboplatin Dosing

- Used $^{51}\text{Cr-EDTA}$ clearance for GFR when Calvert came up with the formula

- $^{51}\text{Cr-EDTA}$ assessments not usually done

- All GFR estimation formulae show a degree of bias and imprecision

- There is no perfect substitute for $^{51}\text{Cr-EDTA}$ GFR, but which is the best out of the imperfect?

Ainsworth et. al. Annals of Oncology 2012; 23: 1845–53
Comparing Different GFR Estimation Formulae For Carboplatin Dosing

<table>
<thead>
<tr>
<th>GFR measure</th>
<th>Carboplatin AUC 5 dose (mg/ml/min), median (IQR)</th>
<th>Percentage error, median (IQR)</th>
<th>APE, median (IQR)</th>
<th>APE &gt; 20%, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium 51 EDTA</td>
<td>580 (480–680)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td>555 (460–705)</td>
<td>−1.9 (−11.0 to 10.9)</td>
<td>10.9 (4.6–19.0)</td>
<td>142 (22)</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>520 (440–630)</td>
<td>−7.7 (−16.8 to 2.7)</td>
<td>12.2 (6.0–20.2)</td>
<td>168 (25)</td>
</tr>
<tr>
<td>Wright</td>
<td>600 (510–730)</td>
<td>5.7 (−3.2 to 18.4)</td>
<td>11.1 (4.7–19.7)</td>
<td>154 (23)</td>
</tr>
<tr>
<td>MDRD</td>
<td>530 (460–630)</td>
<td>−4.6 (−17.0 to 8.1)</td>
<td>13.6 (6.0–22.9)</td>
<td>212 (32)</td>
</tr>
</tbody>
</table>

APE, absolute percentage error; AUC, area under the plasma carboplatin concentration time curve; GFR, glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.

- **Serum creatinine is affected by several factors**

Outline

• Use of body surface area (BSA) in dosing
• Dosing in obesity
• Dosing in amputees
• Estimation of renal function
• Carboplatin dosing using Calvert formula
• Take home messages
Take Home Message (1)

- Do not just use BSA solely
  - Always need to consider other parameters as well
- Use actual body weight to dose chemotherapy for obese patients
- There is a lack of evidence and guideline for dosing of chemotherapy in amputees
  - However, based on the theoretical PK of drugs in amputees and the intention of cure, not unreasonable to use pre-amputation weight and height
Take Home Message (2)

Estimation of renal function

- Cockcroft – Gault has shown to be less bias and more precise formula compared to 3 other formulae
- Not accurate to use creatinine clearance / serum creatinine to estimate GFR in amputees
- In obese patients who weigh >30% above their IBW, use of IBW + 30% can be considered
Take Home Message (3)

- Carboplatin dosing
  - It is most accurate to use $^{51}$Cr-EDTA GFR to calculate carboplatin dose using Calvert formula
  - Cockcroft-Gault formula can be used to estimate the GFR
  - However, it is important to note that estimation of GFR can be affected by several factors
Terima Kasih

Thank You!