Chemotherapy dosing in pediatric patient

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Outline

• Principle of chemotherapy
• Use of BSA in chemotherapy dosing
• Pharmacokinetic consideration
• Chemotherapy dosing in special situation
  – Carboplatin dosing using Calvert formula
  – Obesity
  – Amputees
  – Down’s syndrome
  – Malnutrition
• Conclusion
Basic Principles of Cancer Therapy

• Cancer – unregulated cellular proliferation
• Treatment modalities
  – Surgery
  – Radiation
  – Drug therapy
    • Treatment of choice for disseminated cancers, neoadjuvant
Obstacles to Successful Chemotherapy

• Toxicity to normal cells
• Absence of truly early detection
• Solid tumors respond poorly
• Limited drug access to tumor cells
• Heterogeneity of tumor cells
• Drug resistance
Strategies for Achieving Maximum Benefits from Chemotherapy

• Dose intensity
• Combination
  – Maximum cell kill within acceptable toxicity
  – Suppression of drug resistance
  – Broad coverage against multiple cell lines
  – Intermittent vs. continuous infusion

“Explain with cell cycle kinetics”
Principle of chemotherapy administration

Non-Cell Phase Specific Agents

- Exert their cytotoxic effect throughout the cell cycle
- Cell kill is proportional to dose

Cell Phase Specific Agents

- Toxic to the proportion of cells in the part of the cell cycle in which the agent is active
- Administer as a “continuous infusion”

Begin therapy for kill resting cells, decrease tumor bulk, and recruit more cells into active division
Follow with cell cycle-specific agents
Tumor growth kinetics

Source: DeCherney AH, Nathan L: Current Diagnosis & Treatment Obstetrics & Gynecology, 10th edition: http://www.accessmedicine.com
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Log kill kinetics

- Each course of chemotherapy kills a certain percent of cancer cells not number.
- Cytotoxic chemotherapy kills by 1st order kinetics
- Absolute zero: never reached
- Length of time between cycles: determined by the period of time it takes for normal tissues to rebound from drug toxicities
Optimizing dosing schedules

(Arrows indicate times of drug administration)

CELS REMAINING

TIME

Normal cells

Cancer cells

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Dosing and Administration

• Based on the Patient’s BSA
• Provides a more accurate estimate of cross-species activity and toxicity
• May correlate with cardiac output and subsequent drug distribution and elimination
Body Surface Area

• Pinkel (1958)
  – Retrospective analysis of therapeutic dose per unit weight vs. per unit BSA for 5 drugs
    • Mechlorethamine, methotrexate, 6-mercaptopurine, actinomycin D, triethylene thiophosphoramide
  – 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 until now
Body Surface Area

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

• Mosteller formula: most commonly used
  – Easy to use, remember

\[
m^2 = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}
\]

Body Surface Area

• No pharmacokinetic or efficacy studies to confirm Pinkel’s findings

• Interpatient variability, in terms of pharmacokinetic parameters, still exist
  – Physiological factors
  – Intrinsic factors
  – Environmental factors
Body Surface Area

• Studies: correlation between PK 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

Euro J Cancer 2002; 38;1677–84
Pediatric pharmacokinetic

- Children are not “small adults”
- The effects of chemotherapeutic agents on infants and young children are much different from those occurring in adolescents and adults
- Children differ from adults in each of the four pharmacokinetic stages
Pharmacokinetic considerations

4 PK stages:

– Absorption
– Distribution
– Metabolism
– Excretion
Ontogeny of Body Composition

Kaufman, Pediatric Pharmacology (Yaffe & Aranda, eds) pp. 212-9, 1992
CNS Growth and Development

![Graph showing CNS Volume and BSA growth over age]
Acute Leukemia: Intrathecal dosage

<table>
<thead>
<tr>
<th>อายุ (เดือน)</th>
<th>Methotrexate (mg)</th>
<th>Hydrocortisone (mg)</th>
<th>Cytarabine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>12-23</td>
<td>8</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>24-35</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>≥36</td>
<td>12</td>
<td>24</td>
<td>36</td>
</tr>
</tbody>
</table>
Pediatric Chemotherapy Dosing

• In adults, dosing is usually based on BSA, a practice that is more historical than scientific.

• Because of differences in PK properties, the chemotherapy dosage derived from adult studies may not accurately predict similar drug exposure in pediatric patients.
Pediatric Chemotherapy Dosing

• When to use BW instead?
• Ratio of BSA to BW is significantly higher in infants and drastically lessens as a child grows
• Infants and young children, BSA can greatly overestimate the dose needed to achieve a desired AUC, whereas BW may be a more accurate predictor of drug exposure
Pediatric Chemotherapy Dosing

• “Rule of 30”: used to adjust a dose from mg/m² to mg/kg
  (Pt with BSA of 1 m² weighs approximately 30 kg)

• This conversion can be problematic, since it sometimes leads to a large variability in calculated chemotherapy dose
Protocol name: ThaiPOG-HB-13LR
Protocol for Low risk hepatoblastoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Desired dose</th>
<th>Route</th>
<th>Day</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin (CDDP)</td>
<td>80 mg/m²/dose</td>
<td>IV drip in 24 hr</td>
<td>1</td>
<td>320 mg/m²</td>
</tr>
<tr>
<td>X 4 Cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Give chemotherapy q 2 weeks, ANC > 1,000 and platelet > 100,000 before start chemotherapy
• Blood for LFT, AFP before each course and record liver size every course
• If BW < 12 kg, calculate chemotherapeutic agent dose per kg [(desired dose/ 30) xBW]
• G-CSF is not necessary, unless the patient has febrile neutropenia from the previous course
Pediatric Chemotherapy Dosing

• BSA-based dosing can be overestimated

• Different studies evaluating the same drug and tumor type may determine to use BW-based dosing in pediatric patients based on age (<12 months or <3 years) or weight (<10, 12, or 30 kg)
### ThaiPOG-WT-1301: Favorable histology

<table>
<thead>
<tr>
<th>ข้อมูล</th>
<th>ตัวยา</th>
<th>ขนาดและวิธีใช้</th>
<th>Day</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ทุก 3 wk</td>
<td>Actinomycin-D</td>
<td>Age &lt; 12 months 0.023 mg/kg IV Age ≥ 12 months 0.045 mg/kg IV BW ≥ 30 kg 1.35 mg/m² IV (Maximum dose 2.3 mg)</td>
<td>1</td>
<td>Wk 0, 3, 6, 9, 12, 15, 18</td>
</tr>
<tr>
<td>ทุก 1 wk</td>
<td>Vincristine1</td>
<td>Age &lt; 12 months 0.025 mg/kg IV Age ≥ 12 months 0.05 mg/kg IV BW ≥ 30 kg 1.5 mg/m² IV (Maximum dose 2 mg)</td>
<td>1</td>
<td>Wk1-10</td>
</tr>
<tr>
<td>ทุก 3 wk</td>
<td>Vincristine2</td>
<td>Age &lt; 12 months 0.034 mg/kg IV Age ≥ 12 months 0.067 mg/kg IV BW ≥ 30 kg 2 mg/m² IV (Maximum dose 2 mg)</td>
<td>1</td>
<td>Wk 12, 15, 18</td>
</tr>
</tbody>
</table>
Pediatric Chemotherapy Dosing

• In neonates, dose reductions of up to 50% are commonly made to offset the immaturity of elimination pathways

• Dose reductions are applied inconsistently across treatment regimens and protocols

• Often are based on toxicity observed in previous studies, rather than on true PK data
Carboplatin

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

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

• Formula based on renal function is derived
  – Dose (mg) = target AUC x (GFR + 25)
• AUC correlates with thrombocytopenic nadir
• AUC of 4-6 for 3 weekly regimen gave rise to manageable hematological toxicity
• AUC of 2 for weekly regimen

J Clin Oncol 1989;7:1748-56
FDA dose capping recommendations

- GFR used in calvert formula should not exceed 125ml/min
- AUC 6 = 900 mg
- AUC 5 = 750 mg
- AUC 4 = 600 mg
- Dosing above the FDA dose capping recommendations is rarely seen with the above dosing recommendations
Dosing chemotherapy in obesity

• 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
Dosing chemotherapy in obesity

• Use actual body weight (ABW) in calculating chemotherapy dose regardless of obesity status for oral and intravenous routes
• Cap the Vincristine to a maximum of 2 mg in CHOP and CVP
• Cap Bleomycin in BEP
Dosing chemotherapy in amputees

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

• Drug metabolism
  – Unlikely to change

• Drug excretion
  – Unlikely to change
Dosing chemotherapy in amputees

• Different methods, so confer with protocol guidelines
• Use original weight and height prior to amputation to calculate BSA
• Use post-surgical weight and original height to calculate BSA
Dosing chemotherapy in amputees

Add the following to the body weight to get the adjusted body weight:

<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>

Subtract noted percent of body weight for amputees.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Doxorubicin</td>
<td>37.5</td>
<td>mg/m²/day IV x 2 days (IV slowly push)</td>
</tr>
<tr>
<td>P: Cisplatin</td>
<td>60</td>
<td>mg/m²/day IV over 6 hours x 2 days</td>
</tr>
<tr>
<td>M: HD MTX</td>
<td>12</td>
<td>gm/m²/day IV over 4 hour (max 20 gm)</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>15</td>
<td>mg/m²/dose IV q 6 h, starting at hr 24 of MTX infusion (≥ 8 doses)</td>
</tr>
</tbody>
</table>

การรักษา osteosarcoma ผู้ป่วยจะได้รับยา neoadjuvant chemotherapy เพื่อลดขนาดของกลุ่มนี้เนื้องอกและดูการตอบสนองของกลุ่มนี้เนื้องอกต่อยาเคมีบำบัดซึ่งเป็น prognostic factor หน่วง และยาเคมีบำบัดสามารถควบคุมเนื้องอกที่ metastasisหลังการผ่าตัดผู้ป่วยจะได้รับ adjuvant chemotherapy ต่ออีกระยะ

**Amputee chemotherapy dosage (ThaiPOG):**
Down’s syndrome

• Down syndrome or constitutional trisomy 21
• Linked to leukemia
• Trisomy 21 likely contributes to the development of *GATA1 mutations*
• Chromosome 21-localized genes
  – Cystathionine-β- synthase (*CBS*)
  – Zinc-copper superoxide dismutase (*SOD1*)
  – Folate metabolism
Down’s syndrome

Effect

• Impaired cytidine deaminase activity
• Increased superoxide dismutase (SOD) activity
• Impaired carbonyl reductase 1 (CBR1) activity
• Increased reduced folate carrier (SLC19A1)
Down’s syndrome

• Treatment-related toxicity: more frequent and severe
• Treated with corticosteroids: increased risk of developing hyperglycemia
• May consider decrease the dose or closely monitor toxicity from therapy
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosage</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine (ARA-C)</td>
<td>IV continuous</td>
<td>200 mg/m²/day or 6.67 mg/kg/day if age &lt; 36 mo</td>
<td>Days 1-4</td>
</tr>
<tr>
<td>Doxorubicin (DOX)</td>
<td>IV continuous</td>
<td>20 mg/m²/day or 0.67 mg/kg/day if age &lt; 36 mo</td>
<td>Days 1-4</td>
</tr>
<tr>
<td>Thioguanine (6TG)</td>
<td>PO</td>
<td>50 mg/m²/dose PO BID 1.65 mg/kg/dose PO BID if age &lt; 36 mo</td>
<td>Days 1-4</td>
</tr>
</tbody>
</table>
| Intrathecal Cytarabine (IT ARA-C) | IT | Age (mo)  
<13  
13-24  
25-35  
≥36 | ARA-C  
20 mg  
30 mg  
50 mg  
70 mg | Day 1 |

**Note**

- For CNS 3 patient: give twice weekly IT cytarabine until CNS is clear for 2 consecutive times. Patient with refractory CNS leukemia following 6 doses of therapy will be managed according to institutional protocol.
- หากสถาบันใดไม่มี 6TG สามารถตัด 6TG ออกได้ โดยให้แค่เพียง cytarabine และ doxorubicin.
Special consideration

• There was a significant relationship between the prevalence of treatment-induced neutropenia and malnutrition (South African J Clin Nutr 2017)

• Malnourish patient:
  BW < 12 kg, chemo dose 2/3
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosage</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (DOX)</td>
<td>IV push over 5 minutes</td>
<td>25 mg/m²/dose</td>
<td>1, 2</td>
</tr>
<tr>
<td>Bleomycin (BLEO)</td>
<td>IV over 10 minutes</td>
<td>5 Units/m²/dose</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Units/m²/dose*</td>
<td>8*</td>
</tr>
<tr>
<td>Vincristine (VCR)</td>
<td>IV push over 1 minute</td>
<td>1.4 mg/m²/dose**</td>
<td>1, 8</td>
</tr>
<tr>
<td>Etoposide (ETOP)</td>
<td>IV over 1 - 2 hours</td>
<td>125 mg/m²/dose</td>
<td>1, 2, 3</td>
</tr>
</tbody>
</table>

**Max dose for vincristine 2.8 mg/dose**
**Conclusion**

- Dose based on BSA may not be the best method for every drug
- 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
Conclusion

• Multiple factors complicate the treatment of cancer in pediatric patients
• Clinicians must take these many factors into account when designing chemotherapy regimens for pediatric patients
• Ultimately, these considerations will enable better care and monitoring of pediatric patients with cancer