Carboplatin
Time to Drop the Curtain on the Dosing Debate

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Faculty Disclosures
Jon Herrington
• Nothing to disclose

Judith Smith
• Nothing to disclose

Scott Soefje
• Speaker’s bureau for Amgen, Easai, and Millennium

Introduction
• Carboplatin dosing is a routine question on the HOPA listserv.
• Issues:
  – No uniform standard in measures to use for the Calvert equation.
  – Changes in laboratory measure of creatinine
  – Recent ASCO white paper on dosing in obese adult patients has changed many attitudes

Objectives
• Review the background and history for dosing carboplatin
• Compare and contrast issues with carboplatin dosing including what body weight and serum creatinine values used in estimation of renal function
• Discuss the challenges of using a standardized approach in dosing carboplatin

Background and History

History of Carboplatin
• Carboplatin
  – FDA approved 1989
  – Advanced ovarian cancer
    – Single agent 360 mg/m² IV q 4 weeks
  – Kinetics
    • Linear kinetics
    • 65-70% renal clearance within 24 hours
  – Toxicity
    • Dose limiting thrombocytopenia

Paraplatin prescribing information, Bristol Myers, 1989
History of Carboplatin Dosing

- 1982: BSA dosing completed by Calvert
- 1984-85: Egorin formula
- 1989: Calvert formula
- 1993: Newell revised Calvert formula for children
- 1995: Chatelut equation based on patient variables and creatinine
- Variety of different updates/changes to equations

Egorin Formula

- Egorin 1984
  - Correlated
    - Renal function to thrombocytopenia
    - AUC to thrombocytopenia
    - Total carboplatin clearance to CrCl
  - Greater thrombocytopenia in heavily pretreated patients
  - Clearance = dosage / AUC
- Egorin formula 1985
  - 24 hr CrCl, BSA, pretreatment platelet count, platelet nadir desired, status of prior chemo
  - Two 24hr CrCl completed within one week prior to carboplatin
  - Used mean result in equation

Demographics

<table>
<thead>
<tr>
<th></th>
<th>N = 24 (44 courses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>53 (33 - 77)</td>
</tr>
<tr>
<td>Sex</td>
<td>13 female 11 male</td>
</tr>
<tr>
<td>CrCl &lt; 60 mL/min</td>
<td>10</td>
</tr>
</tbody>
</table>


Relationship Between Predicted and Observed Platelets (n = 24 patients; 44 courses)


Why don’t we use this equation?

- Variables to consider
  - BSA
  - 24 CrCl collections
  - Pretreatment and expected platelet level
  - Chemotherapy history
- What is the optimal platelet nadir goal?
- Dose in mg/m²
Carboplatin Dosage: Prospective Evaluation of a Simple Formula Based on Renal Function
Calvert AH, Newell DR, Gumbrell LA, et al.

• Three part study
  1. Formula derived from retrospective data
  2. Formula tested in prospective trial
  3. Formula refined

• Patient Characteristics (n=49)
  – Mean age (range): 56 (17-78)
  – GFR range: 33-136 mL/min
    • GFR estimated using $^{51}$Cr-EDTA


Calvert Formula for Adults

• Derived from Dose = AUC x CL
• Dose (mg) = AUC (GFR + 25)
  – “25” denotes nonrenal clearance
  • Most likely due to irreversible tissue binding


What is the debate?

• Formula is simple
• BSA did not correlate with nonrenal clearance or GFR
  – Did not report weight or BSA in study
• $^{51}$Cr-EDTA is expensive and not readily available
• Do you know how to predict / calculate /estimate glomerular filtration rate / creatinine clearance?

Chatelut

• Purpose of formula to provide an accurate carboplatin clearance
  – Without creatinine clearance calculation
  – Without the use of radioisotopes
• Two part study
  – 34 patients to develop formula
  – 36 patients for prospective evaluation of formula
  – Calculated GFR by $^{51}$Cr-EDTA, $^{99}$mTc-DTPA and CrCl by Cockcroft-Gault
  – Compare methods with actual carboplatin clearance


Chatelut - Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Formula Establishment (n=34)</th>
<th>Prospective Evaluation (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>23 male</td>
<td>23 male</td>
</tr>
<tr>
<td></td>
<td>11 female</td>
<td>13 female</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>64 (27-82)</td>
<td>54 (23-84)</td>
</tr>
<tr>
<td>Cr (mean, range)</td>
<td>1.5 (0.6-4.0)</td>
<td>1.2 (0.6-2.6)</td>
</tr>
<tr>
<td>Kg (mean, range)</td>
<td>70 (43-112)</td>
<td>66 (44-90)</td>
</tr>
</tbody>
</table>

Chatelut Formula

• Carboplatin Clearance = (0.134 x kg) + ((1 if male, 0.686 if female) x 218 x kg) x (1 - (0.00457 x age)) / serum creatinine (mg/dl) x 88.4
• Dose = CL x AUC


Carboplatin Clearance Prediction

<table>
<thead>
<tr>
<th>Equation</th>
<th>Bias, % error</th>
<th>Precision, absolute % error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective data formula</td>
<td>2 (-25 to 30)</td>
<td>10 (0 to 30)</td>
</tr>
<tr>
<td>GFR ((^{51})Cr-EDTA) mL/min + 25</td>
<td>-3 (-32 to 41)</td>
<td>13 (1 to 41)</td>
</tr>
<tr>
<td>GFR ((^{99})mTc-DTPA) mL/min + 25</td>
<td>-23 (-48 to 69)</td>
<td>27 (1 to 69)</td>
</tr>
<tr>
<td>CrCl mL/min + 25</td>
<td>-17 (-42 to 26)</td>
<td>18 (1 to 42)</td>
</tr>
</tbody>
</table>


Why isn’t Chatelut formula utilized?

• Complicated equation
• Wide variance with bias and precision with “standard” \(^{51}\)Cr-EDTA
• Subsequent studies have failed to support findings

GFR vs. CrCl for Carboplatin

• Numerous studies with various conclusions
• Isotope GFR determination will ALWAYS be preferred over estimation
  – Expensive
  – Requires blood sampling
  – Not readily available
• Which is the ideal method to mimic carboplatin clearance (GFR + 25) in the Calvert?
  – Cockcroft-Gault CrCl
  – MDRD GFR
  – CKD-EPI GFR

Overestimation of Carboplatin Doses is Avoided by Radionuclide GFR Measurement

• Study aim: Accuracy of 3 equations in carboplatin dose calculations
• \(^{51}\)Cr-EDTA compared with C-G, MDRD 4 variable, and CKD-EPI
  – All equations standardized to BSA (Haycock)
• Creatinine measured by kinetic Jaffe method, calibrated against IDMS values
• 288 patients studied; only 175 received carboplatin

Demographics and Clinical Data, n=288

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : female, %</td>
<td>56:44</td>
</tr>
<tr>
<td>Age, years</td>
<td>66±12 (21-93)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72±17 (31-131)</td>
</tr>
<tr>
<td>BSA, m(^{2})</td>
<td>1.8±0.3 (1.1-2.6)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.0±0.54 (0.68-7.21)</td>
</tr>
<tr>
<td>(^{51})Cr-EDTA GFR (mL/min per 1.73m(^{2}))</td>
<td>63±20 (5-128)</td>
</tr>
<tr>
<td>MDRD eGFR (mL/min per 1.73m(^{2}))</td>
<td>76±23 (8-149)</td>
</tr>
<tr>
<td>CKD-EPI eGFR (mL/min per 1.73m(^{2}))</td>
<td>77±23 (7-138)</td>
</tr>
<tr>
<td>Cockcroft-Gault CrCl (mL/min per 1.73m(^{2}))</td>
<td>71±24 (9-153)</td>
</tr>
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### Carboplatin Doses, mean (range)

<table>
<thead>
<tr>
<th>GFR (mL/min 1.73m²)</th>
<th>⁵¹Cr-EDTA</th>
<th>Cockcroft-Gault</th>
<th>MDRD</th>
<th>CKD-EPI</th>
</tr>
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<tbody>
<tr>
<td>Overall (n = 175)</td>
<td>458 (230–790)</td>
<td>503 (250–1120)</td>
<td>519 (280–1150)</td>
<td>529 (270–1020)</td>
</tr>
<tr>
<td>&lt; 30 (n = 7)</td>
<td>258 (230–290)</td>
<td>295 (250–370)</td>
<td>310 (280–360)</td>
<td>307 (270–360)</td>
</tr>
<tr>
<td>30-59 (n = 84)</td>
<td>383 (270–500)</td>
<td>445 (300–790)</td>
<td>464 (280–700)</td>
<td>472 (290–700)</td>
</tr>
<tr>
<td>60-89 (n = 85)</td>
<td>511 (350–720)</td>
<td>545 (330–1120)</td>
<td>563 (380–1150)</td>
<td>575 (380–1020)</td>
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Craig AI, et al. Br J Cancer 2012;107;1310-6

### Trial Summary

- Exogenous filtration marker, ⁵¹Cr-EDTA, preferred method
- If unavailable, use Cockcroft-Gault

### Summation

- Correlation between carboplatin clearance and thrombocytopenia
- Correlation between renal function and carboplatin AUC
- Need to recognize weakness / strengths of these formulae

### What values to use in C-G equation?

- What body weight should be used for calculating CrCl?
- In what population is it appropriate to use an adjusted body weight?
- Is it appropriate to round SCr to pre-specified values in elderly or cachectic patients?
Cockcroft-Gault Method

- Gold Standard for CrCl estimation in adults
- Study population
  - Developed in 236 adult non-obese males
  - Mean ± SD CrCl was 72.7 ± 36.6 mL/min
  
  \[
  \text{Cockcroft-Gault} = \frac{140 - \text{age}}{\text{weight (kg)}} \times (0.85 \text{ if female}) \times \text{SCr} \times 72
  \]
  
- Validated in several studies in multiple patient populations

Cockcroft DW Gault MH., Nephron 1976; (16) 31-41

Weight Input for C-G

- Actual Body Weight (ActBW)
  - Designed and validated using ActBW.
  - Should be used for most patients.
- Adjusted Body Weight (AdjBW)
  - Appropriate for patients with BMI>30 kg/m²
  - IBW + 30% (ActBW – IBW)
- Ideal Body Weight (IBW)
  - Underestimates CrCl in most patients
  - Exception underweight may overestimate

What to do with SCr < 0.7 mg/dL?

- SCr levels are low in patients with low muscle mass, especially the elderly.
- Poor accuracy in patients with low SCr.
- Rounding to 1.0 mg/dL results in underestimation of CrCl.
  - 0.8 mg/dL common as well
- Use of reported SCr overestimates CrCl.

NO CLEAR DATA TO SUGGEST EITHER METHOD CLINICAL JUDGEMENT IS NECESSARY FOR INDIVIDUAL PATIENTS

Methods of Serum Creatinine Detection

- Jaffe Method
  - Interference by acetoacetate, pyruvate, ketoads
- Kinetic Picrate Method
  - Analysis at specific time point
- Enzymatic Methods
  - Reaction of creatinine to form ammonia
  - 10x more costly than picrate.
  - Inaccurate at low SCr concentrations.
  
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Methods of Serum Creatinine Detection and Quantification

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<td>2. Kinetic Picrate Method</td>
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<td>3. Enzymatic Method</td>
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NKDEP Standardization Program

- Started in 2005 in response to wide inter-laboratory variation in reported SCr
- Isotope dilution mass spectrometry (IDMS)
  - Requires manufacturers to standardize assay kits to IDMS standard values
  - SCr should be reported as X.XX mg/dL
    - Although poorly adapted into practice
    - Values are 5-20% lower than those previously reported
    - Upper limit of normal reference range of serum creatinine now <1.0 mg/dL
    - Did not replace currently used methods.


IDMS SCr in Cockcroft-Gault

- Because patient samples are no longer available for correction validation, C-G cannot be re-expressed.
- IDMS SCr would need be converted to Non-IDMS SCr before input into the equation.
  - Requires each assay manufacturer to validate conversion
  - Ortho Clinical Diagnostics
    - Non-IDMS SCr (mg/dL) = IDMS SCr (mg/dL) x 1.065 + 0.067
      - (This is equation of line for linearity in analytical assays)

Carboplatin Questions

- A common question on the HOPA listserv:
  - What body weight do you use in calculation of carboplatin dosing?
  - Do you adjust creatinine clearance for low serum creatinine?
  - Do you cap doses of carboplatin?

HOPA/NCCN Carboplatin Dosing Survey

- Conducted in Spring of 2010
- 525 respondents
  - 80.5% pharmacists
  - 18.9% physicians
- 96.5% of all respondents use the Calvert equation
- 94.1% use estimated creatinine clearance

Which method do you use to calculate creatinine clearance?

- A. Cockcroft-Gault
- B. Jelliffe
- C. MDRD
- D. Other
For obese patients (defined as patients with actual body weight > 30% of ideal body weight) which body weight do you use?

A. Ideal  
B. Actual  
C. Adjusted  
D. Other  

Let’s weigh-in on weight...

- ASCO guidelines recommend actual weight for BSA calculations  
- Does not reflect carboplatin AUC dosing  
  - For obese patients, use adjusted body weight to calculate CrCl with C-G  
  - 4 separate studies  

Question #2: Which body weight to use?

For serum creatinine levels less than the lower limit of normal by the method your institution uses to measure creatinine, do you round the reported level?

A. Yes  
B. No  
C. I do not know  

Does your institution use the IDMS method to measure serum creatinine?

A. Yes  
B. No  
C. I do not know  

Kwaas O. Lung Cancer 2013;75:54-8  

Question #3: Serum Creatinine Rounding
Do you cap creatinine clearance?

A. Yes
B. No
C. I do not

If you cap creatinine clearance values, what value do you use?

A. 100 mL/min
B. 120 mL/min
C. 125 mL/min
D. 150 mL/min
E. We do not cap creatinine clearance values

Question #4: Capping Doses

Cap or not to cap... the GFR

- Capping BSA is not recommended for curative patients
- For CrCl / GFR equations, it makes some sense
  - Accurate weight and creatinine values
  - Adjust values for obese or cachectic patients
- What do the studies show?

GFR Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>(^{51}\text{Cr-EDTA GFR (mL/min)})</th>
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<tbody>
<tr>
<td>Craig, et al</td>
<td>mean±SD 63±20 range 5-128 per 1.73m²</td>
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<td>Calvert, et al</td>
<td>range 33-136</td>
</tr>
<tr>
<td>Millward, et al</td>
<td>range 39-179</td>
</tr>
<tr>
<td>Ainsworth, et al</td>
<td>median 90 range 23-176</td>
</tr>
</tbody>
</table>

Conclusions

- Obvious need to standardize methods for calculating carboplatin
- Cockcroft-Gault is the preferred equation to calculate creatinine clearance
  - Use adjusted weight in obese patients
  - Round-up low creatinine values to your institutional lower limit of normal
- Capping of CrCl at 125 mL/min is recommended for majority of patients
