The right dose to the right patient – chemotherapy adaption in specific situations

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• treatment of obese patients
• treatment in renal insufficiency and dialysis pts
• liver function and dosing
• include some dosing aspects for targeted agents
The problem (1)

male, 26 years
BW 145 kg, 1.92 m height → BSA: > 2.5 m²

Diagnosis: metastatic testicular cancer with pulmonary lesions
Curative chemotherapy planned

Dosing of chemotherapy (PEB)

- P cisplatinum: renal, oto- and neurotoxicity increased?
- E etoposide: myelotoxicity, risk for secondary leukemia?
- B bleomycin: more pulmonary toxicity?
Population: Adult obese patients with cancer
- Greater than 60% of adults in US have body mass index (BMI) greater than 25 and are considered overweight or obese

Chemotherapy dosing is based on patient’s estimated BSA using several formulae which include the body weight

Studies confirm importance of full weight-based doses of cytotoxic chemotherapy (at least in the curative setting)
- Up to 40% of obese pts receive limited doses not based on actual body weight
- Chemotherapy dosing limited at 2m2 BSA
• An Expert Panel reviewed relevant medical literature
• Database searched:
  ➢ MEDLINE
  ➢ Cochrane Collaboration Library
• Data parameters:
  ➢ January 1966 – October 2010
• Ongoing clinical trials monitored
  ➢ The National Cancer Institute’s (NCI) database of clinical trials
  ➢ National Library of Medicine’s clinicaltrials.gov

J.J. Griggs, April JCO 2012
Recommendation #1.1:

• Use actual body weight to calculate cytotoxic chemotherapy dose regardless of obesity status

• No evidence that short- or long-term toxicity is increased with full weight-based doses

• In patients receiving chemotherapy dosed on the basis of actual body weight, myelosuppression is the same or less pronounced in obese patients with cancer than in non-obese patients
Recommendation #2.1:

- Use weight-based doses especially in curative setting

- **Reduced doses may result in poorer disease-free and overall survival rates**
  - Supporting data in patients with breast cancer
  - Dose-response relationship exists for many other responsive malignancies e.g., lung and gynecologic cancers
  - Most data from treatment of early-stage disease

- Data in advanced disease (palliative) setting are limited
4856 pts. in MRC colorectal cancer trials:

- 2002 (45%) normal weight
- 1774 (34%) overweight
- 880 (18%) obese

- Reduced doses:
  - normal weight 6%,
  - overweight 17%,
  - obese 55% (sig)

- Toxicity: normal weight 21%, overweight 20%, obese 17%

- Toxicity in obese pts: full dose 17%, reduced dose 16%

- Survival normal versus reduced dose HR 1.16

Recommendation #4.1:

- Consider fixed dosing only with selected cytotoxics
  - Examples: carboplatin --> use GFR based dosing
  - Bleomycin always fixed dose
  - Oxaliplatin? Limit at 2m2?

- Due to neurotoxicity concerns, cap vincristine at maximum of 2.0 when used as single agent or part of CHOP* or CVP**

  * CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
  ** CVP = cyclophosphamide, vincristine, prednisone
Recommendation #5.1:

- **Calculate BSA with any standard formula**
- No evidence supporting one formula for calculating body surface area over another

**Common Formulae**

**BSA**

- **Boyd Formula**
  - \[ \text{BSA} \ (m^2) = 0.0003207 \times Ht \ (cm)^{0.3} \times \text{weight} \ (g) \times (0.7285 - (0.0188 \times \log_{10} \text{weight(g)})) \]

- **DuBois and DuBois Formula**
  - \[ \text{BMS} \ (m^2) = \text{Wt(Kg)}^{0.425} \times \text{Ht(cm)}^{0.725} \times 0.007184 \]

- The full guideline, data supplements, patient guide, a dosing table, podcasts, FAQs, and other resources are available at [www.asco.org/guidelines/wbd](http://www.asco.org/guidelines/wbd)
- The patient guide is also available at [http://www.cancer.net](http://www.cancer.net)
The problem (2)

female patient 69 years; 
metastatic colorectal cancer (liver, lung, lymphatic nodes) 
GFR 35 ml/min, no known renal disease

Dosing of chemotherapy (XELOX planned)

Capecitabine - increased toxicity due to reduced clearance? 
Oxaliplatin - dose reduction necessary for renal toxicity or due to potential increase of side effects?
French study of 4684 pts presenting at 15 cancer centers in 2004 52% had decreased renal function according to MDRD formula, half were treated with drugs requiring dose adaptation based on renal function.

- Serum Creatinine >110 ml/min
- Creatinine Clearance <90 ml/min: Crockcroft-Gault
- Creatinine Clearance <90 ml/min: aMDRD

Graph showing patients (%) by types of cancer: All, Breast, Colorectal, Lung, Ovarian, Prostate.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Patients with risk factors for developing kidney disease: patients should be monitored</td>
<td>More than 90</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage and normal GFR</td>
<td>More than 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage and mild decrease in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (dialysis or kidney transplant needed)</td>
<td>Less than 15</td>
</tr>
</tbody>
</table>
Decreased renal clearance increases exposure to all drugs not only cytotoxics.
## Nephrotoxic Cytotoxics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Toxicity</th>
<th>Mechanism</th>
<th>Preventive Strategies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin</strong></td>
<td>ArF; tubular damage; renal concentration defect; polyuria; hypomagnesemia; rarely HUs</td>
<td>Toxic damage to the s3 segment of proximal Tubule, loop of Henle, and distal tubules</td>
<td>volume infusion, amifostine</td>
<td>Avoid further use; volume infusion; magnesium repletion; dialysis for uremia</td>
</tr>
<tr>
<td><strong>Ifosfamide</strong></td>
<td>subclinical tubular damage in most Patients; severe electrolyte depletion; nephrogenic diabetes insipidus;</td>
<td>Proximal tubular damage by metabolites such as chloracetaldehyde; total dose-related toxicity</td>
<td>Mesna (questionable benefit); avoid concomitant cisplatin</td>
<td>Bicarbonate; phosphate; electrolyte repletion</td>
</tr>
<tr>
<td><strong>Mitomycin C</strong></td>
<td>TTP and HUs often presents as ArF</td>
<td>Thrombotic microangiopathic lesions; glomerular infarction</td>
<td>No established preventive measures</td>
<td>Plasmapheresis; Staphylococcus A column immunoadsorption</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>renal failure with high dose therapy (1.8%)</td>
<td>Precipitation of methotrexate and 7-hydroxymethotrexate into renal tubules</td>
<td>volume infusion; alkalinization with sodium bicarbonate; leucovorin rescue</td>
<td>supportive measures; Dialysis; carboxypeptidase-G2</td>
</tr>
</tbody>
</table>
## Nephrotoxic Cytotoxics

<table>
<thead>
<tr>
<th>Drug</th>
<th>% dose excreted in urine</th>
<th>90–60 mL/min</th>
<th>60–30 mL/min</th>
<th>30–15 mL/min</th>
<th>&lt;15 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>90</td>
<td>50 to 120 mg/m² every 3 to 6 weeks</td>
<td>Not recommended, however if unavoidable an appropriate dose should be used: 25 to 60 mg/m² every 3 to 6 weeks</td>
<td>Not recommended, however if unavoidable an appropriate dose should be used: 25 to 60 mg/m² every 3 to 6 weeks</td>
<td>Not recommended, however if unavoidable an appropriate dose should be used: 25 to 60 mg/m² every 3 to 6 weeks</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>95</td>
<td>Adjust according to patient using a formula such as the Calvert formula.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>54</td>
<td>85 or 100 mg/m² every 2 weeks, or 130 mg/m² every 3 weeks</td>
<td></td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>55-88</td>
<td>30 to 50 mg/m²</td>
<td>24 to 40 mg/m²</td>
<td>15 to 25 mg/m²</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>45</td>
<td>dose/day: 1.5 to 3 g/m²; dose/cycle: 5 to 10 g/m²</td>
<td></td>
<td></td>
<td>dose/day: 1.13 to 2.25 g/m² dose/cycle: 3.75 to 7.5 g/m²</td>
</tr>
</tbody>
</table>
Carboplatin dosing:

How to choose the target AUC?

⇒ Estimated hematotoxicity (neutropenia, thrombocytopenia)

• 383 pts with carboplatin - based therapies
  PK-PD model correlated to hematoxicity

⇒ chosen combination effects risk of grade 3/4 thrombopenia
  (low risk with paclitaxel, higher risk with gemcitabine)

A. Schmitt et al, JCO 2010
Simulated percentage of patients experiencing hematotoxicity according to the final models

Thrombocytopenia grade 3 or 4.

Gold, red, and blue indicate previous chemotherapy; gray indicates no chemotherapy.

Neutropenia grade 4.

VP16, etoposide; AUC, area under the curve.

Schmitt A et al. JCO 2010;28:4568-4574
Targeted agents can effect renal function

Kelly et al., 2009
The special case: Chemotherapy in dialysis pts

- Dose reduction to avoid side effects - not to protect the kidneys
- the time between chemotherapy and dialysis is crucial
## Need for dosage adjustment in hemodialysis patients according to Launay-Vacher et al. and Lichtman et al.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Launay-Vacher et al.</th>
<th>Lichtman et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Yes</td>
<td>Not mentioned in the recommendations</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>No</td>
<td>No data</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>No data</td>
<td>No</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>No</td>
<td>No data</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vinorelbine i.v.</td>
<td>Yes</td>
<td>No data</td>
</tr>
</tbody>
</table>

Janus et al., Ann Oncol, 2010
The problem (3)

58 years, male
colorectal cancer with liver metastases, k-ras wildtype
Immediate response to chemotherapy required due to very advanced disease
total bilirubin 2.5 mg/dl, transaminases 200-300 U/l

Dosing of chemotherapy

FOLFIRI + Cetuximab

5FU - reduction necessary?
Irinotecan - at all possible despite brb ↑?
Cetuximab - no problem?
Pharmacological tasks of the liver

- **Absorption**: 1\textsuperscript{st}-pass Effekt \uparrow
- **Distribution**: Proteinsynthesis \downarrow \rightarrow proteinbinding \downarrow
- **Metabolismus**: CYP, NAT, ST, GST
- **Elimination**: UGT, MDR1 (p-glykoproteine)
**Paclitaxel**

Up to a bilirubin of 80 µmol/L dose adaption can follow the following recommendations:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ALT/AST</th>
<th>Bilirubin</th>
<th>Dose level</th>
<th>Predefined</th>
<th>Model-derived recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt; 2.6 x ULN</td>
<td>≤ 1.25 x ULN</td>
<td>0</td>
<td>175</td>
<td>*</td>
</tr>
<tr>
<td>II</td>
<td>2.6-10 x ULN</td>
<td>≤ 1.25 x ULN</td>
<td>0</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>III</td>
<td>&lt; 10 x ULN</td>
<td>1.26-2.0 x ULN</td>
<td>0</td>
<td>175</td>
<td>115</td>
</tr>
<tr>
<td>IV</td>
<td>&lt; 10 x ULN</td>
<td>2.1-3.5 x ULN</td>
<td>-1</td>
<td>135</td>
<td>100</td>
</tr>
<tr>
<td>V</td>
<td>&lt; 10 x ULN</td>
<td>≥ 3.6-10 x ULN</td>
<td>-2</td>
<td>110</td>
<td>80</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>AST or ALT</th>
<th>Serum-Bilirubin</th>
<th>Paclitaxel dose reduction</th>
<th>3-weekly dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2-times ULN</td>
<td>&lt;20µmol/L (1.5mg/dl)</td>
<td>-20%</td>
<td>135mg/m²</td>
</tr>
<tr>
<td>&lt;10-times ULN</td>
<td>&gt;20µmol/L (1.5mg/dl)</td>
<td>-50%</td>
<td>90mg/m²</td>
</tr>
<tr>
<td>&gt;10-times ULN</td>
<td>&gt;80µmol/L (5mg/dl)</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>
**Gemcitabine**

- Clinical study of pts with different severity of liver dysfunction

Gemcitabine 1000mg/m² d1/8, Capecitabine 650mg/m² d1-15, q3w

<table>
<thead>
<tr>
<th>COHORT</th>
<th>Serum-Bilirubin (µmol/L)</th>
<th>ASAT/ALAT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; ULN</td>
<td>≤ 2 times ULN</td>
</tr>
<tr>
<td>2</td>
<td>ULN to ≤ 30</td>
<td>≤ 10 times ULN</td>
</tr>
<tr>
<td>3</td>
<td>30 to ≤ 50</td>
<td>≤ 10 times ULN</td>
</tr>
<tr>
<td>4</td>
<td>50 to ≤ 80</td>
<td>≤ 10 times ULN</td>
</tr>
</tbody>
</table>

- Bilirubin 30-50 µmol/L → 20% dose reduction
- Bilirubin 50-80 µmol/L → 33% dose reduction
Irinotecan

- Clearance negatively correlated to bilirubin, AP

Dose recommendation:

<table>
<thead>
<tr>
<th>Time</th>
<th>Standard dose</th>
<th>1.5-3.0xULN</th>
<th>3.1-5.0xULN</th>
<th>1.5-3.0xULN + AST/ALT &gt;5xULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-weekly</td>
<td>350mg/m²</td>
<td>200mg/m²</td>
<td>100mg/m²</td>
<td>Bili &gt;5xULN → not recommended</td>
</tr>
<tr>
<td>1-weekly</td>
<td>125mg/m²</td>
<td>60mg/m²</td>
<td>50mg/m²</td>
<td>40mg/m²</td>
</tr>
</tbody>
</table>

¹Raymond et al, J Clin Oncol 2002;20: 4303-12.
Sorafenib

- orally applicable multi-tyrosinkinase inhibitor
- hepatic metabolisation via CYP3A4
- hepatic elimination via the bile fluid, particularly UGT1A9-mediated glucuronidation
- Recommended dose reductions¹:
  - Bilirubin 1.5-3.0xULN, any AST → 200mg bid
  - Albumin <2.5mg/dL (any Bilirubin/AST) → 200mg qd
  - Bilirubin >3.0xULN → Sorafenib not tolerated

¹ Miller et al, J Clin Oncol 2009(27): 1800-05
# Tyrosine kinase inhibitors and mTOR inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Child-Pugh A</th>
<th>Child-Pugh B</th>
<th>Child-Pugh C</th>
<th>References</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>400mg/d</td>
<td>400mg/d</td>
<td><strong>300mg/d</strong></td>
<td>Ramanathan, JCO 2008;26:563-9</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>75mg/d</td>
<td>75mg/d</td>
<td><strong>unknown</strong></td>
<td>Miller, JCO 2007;25:3055-60</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>50mg/d (4/2)</td>
<td>50mg/d (4/2)</td>
<td><strong>unknown</strong></td>
<td>Bello, Cancer Chemother Pharm 2010;66:699-707</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>400mg bid</td>
<td><strong>200mg bid or not at all</strong></td>
<td><strong>Not recommended</strong></td>
<td>Miller, JCO 2009;27:1800-5</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1250mg/d</td>
<td><strong>unknown</strong></td>
<td><strong>unknown</strong></td>
<td>Medina, Clin Ther 2008;30:1426-47</td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>25mg/wk</td>
<td>25mg/wk</td>
<td><strong>10mg/wk</strong></td>
<td>Boni, Semin Oncol 2009;36(suppl):S18-25</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>10mg/d</td>
<td>5gm/d</td>
<td><strong>unknown</strong></td>
<td>Kovarik, Clin Phamacol Ther 2001;70:425-30</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **CYP3A4**

- Imatinib 400mg/d (child-Pugh A and B) for Child-Pugh C 300mg/d
- Erlotinib 75mg/d (child-Pugh A and B) for Child-Pugh C unknown
- Gefitinib 250mg/d (child-Pugh A and B) for Child-Pugh C unknown
- Sunitinib 50mg/d (4/2) (child-Pugh A and B) for Child-Pugh C unknown
- Sorafenib 400mg bid (child-Pugh A) for Child-Pugh C **Not recommended**
- Lapatinib 1250mg/d (child-Pugh A) for Child-Pugh C unknown
- Temsirolimus 25mg/wk (child-Pugh A and B) for Child-Pugh C **10mg/wk**
- Everolimus 10mg/d (child-Pugh A) for Child-Pugh C unknown

**References:**
- Ramanathan, JCO 2008;26:563-9
- Miller, JCO 2007;25:3055-60
- Bello, Cancer Chemother Pharm 2010;66:699-707
- Miller, JCO 2009;27:1800-5
- Boni, Semin Oncol 2009;36(suppl):S18-25
- Kovarik, Clin Phamacol Ther 2001;70:425-30
Conclusion

Multiple situations in routine daily practice may require dose adaptation of chemotherapy and/or targeted agents.

Most common situations are renal and hepatic insufficiency.

Data on safety of dose modifications are limited, but careful action is always required.

In contrast to dose reductions in the above situations, for obese patients no routine change of BSA-based chemotherapy dosing is required.
Special thanks

Stephan Balabanov,
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