APPROPRIATE CHEMOTHERAPY DOSING FOR OBESE ADULT PATIENTS WITH CANCER

Clinical Practice Guideline
Introduction & Context

• 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 (*see slides 15 and 16*)

• Studies confirm safety and importance of full weight-based doses of cytotoxic chemotherapy

• Many overweight and obese patients receive limited chemotherapy doses
  ➢ Up to 40% receive limited doses not based on actual body weight
Introduction, cont’d

• Even when chemotherapy doses are calculated according to actual body weight, obese patients are less likely to experience toxicity
• Reductions in standard dose and dose intensity may compromise disease-free and overall survival, particularly in curative setting

The evidence
• Compelling body of evidence supports relationship between selection of dose in this population and
  ➢ toxicity
  ➢ pharmacokinetic correlates of dose selection
Introduction, cont’d

The evidence, cont’d

• Many published clinical trials do not present the planned chemotherapy dosing or delivered dose intensity.

• Few randomized controlled trials (RCTs) and pharmacokinetic studies address optimal methods of dose calculation and delivery.
Guideline Methodology: Systematic Review

• An Expert Panel reviewed relevant medical literature
• Databases searched:
  ➢ MEDLINE
  ➢ Cochrane Collaboration Library
➢ Date parameters:
  ➢ January 1966 – October 2010
➢ Ongoing clinical trials monitored
  ➢ The National Cancer Institute’s (NCI) PDQ database of clinical trials
  ➢ National Library of Medicine’s clinicaltrials.gov
Clinical Questions

1. Is there evidence that full weight-based dosing increases toxicity in obese patients with cancer?
2. Is there evidence that less than full weight-based dosing compromises efficacy in obese patients with cancer?
3. If an obese patient experiences high-grade toxicity, should chemotherapy doses or schedule be modified differently from modifications used for nonobese patients with cancer?
4. Is the use of fixed-dose (dose prescribed independent of weight or body surface area [BSA]) cytotoxic chemotherapy ever justified? Are there unique dosing considerations for certain chemotherapeutic agents?
5. How should BSA be calculated? Specifically, what is the best formula for use with the obese patient with cancer?
6. What is the role of pharmacokinetic and/or pharmacogenetic factors when determining optimal chemotherapy dose and delivery (bolus, infusional, therapeutic drug monitoring) for obese patients with cancer?
RECOMMENDATIONS
Does weight-based dosing increase toxicity?

Recommendation # 1.1

• Use actual body weight to calculate cytotoxic chemotherapy (IV and oral) 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
Does weight-based dosing increase toxicity? cont’d

Recommendation #1.2

• Use full weight-based chemotherapy dosing for morbidly obese patients with cancer
  ➢ Consider other comorbidities
• Data extremely limited about optimal dose selection in this group and other special subgroups
• Use same principles regarding dose selection as for obese patients
• More studies needed to evaluate optimal agents for obese and morbidly obese patients with cancer
• Available information points to applying same principles for morbidly obese and overweight as for obese patients with cancer
Additional information – toxicity

With doses calculated using actual body weight, there is:

• No increase in hematologic toxicity
  - Example 1: full weight-based doses of cyclophosphamide/methotrexate/5-FU – leukocyte nadirs higher among obese than non-obese patients with breast cancer
  - Example 2: full weight-based doses of doxorubicin/cyclophosphamide – febrile neutropenia decreased as BMI increased in patients with breast cancer

• No increase in non-hematologic toxicity

Is efficacy compromised with weight-based dosing?

**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 setting are limited

*(recommendation continued on next slide)*
Is efficacy compromised with weight-based dosing? - cont’d

- Although data can’t currently address this question for all cancer types, in the absence of data demonstrating sustained efficacy for reduced dose chemotherapy, a prudent approach is providing full weight-based chemotherapy dosing, especially with those treated with curative intent.
Should doses be modified (differently than for nonobese patients) if toxicity occurs?

Recommendation #3.1

- Follow same guidelines for dose reduction regardless of:
  - obesity status
  - type/severity of toxicity
  - comorbid conditions
  - treatment intent (cure or palliation)
- Greater dose reductions for obese patients not evidence-based
- If dose reduced, consider resuming full weight-based dose if/when toxicity resolved
- Exercise judgment for patients with Grade 3 or 4 chemotherapy toxicity
  - Obesity alone should not alter such clinical judgment
Is a fixed dose ever justified for obese patients?

Recommendation #4.1

• Consider fixed dosing only with select cytotoxics
  ➢ Examples: carboplatin and bleomycin
• Due to neurotoxicity concerns, cap vincristine at maximum of 2.0 when used as part of CHOP* or CVP**

*CHOP = cyclophosphamide, hydroxydoxorubicin (doxorubicin), vincristine, prednisone
**CVP = cyclophosphamide, vincristine, prednisone
How should BSA be calculated?

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
  \[ \text{BSA} (\text{m}^2) = 0.0003207 \times \text{Ht} (\text{cm})^{0.3} \times \text{weight(g)}^{(0.7285 - (0.0188 \times \log_{10} \text{weight(g)}))} \]
- DuBois and DuBois Formula
  \[ \text{BSA}(\text{m}^2) = \text{Wt(kg)}^{0.425} \times \text{Ht(cm)}^{0.725} \times 0.007184 \]
Formulae, cont’d

- **Gehan and George Formula**
  
  \[ \text{BSA}(\text{m}^2) = \text{Wt}(\text{kg})^{0.51456} \times \text{Ht}(\text{cm})^{0.42246} \times 0.0235 \]

- **Haycock, et al. Formula**
  
  \[ \text{BSA}(\text{m}^2) = \text{Wt}(\text{kg})^{0.5378} \times \text{Ht}(\text{cm})^{0.3964} \times 0.024265 \]

- **Mosteller (Adults and Children) Formula**
  
  \[ \text{Square root}[(\text{Ht(cm)} \times \text{Wt(kg)})/3600] \text{ OR} \]
  
  \[ \text{Square root}[(\text{Ht(in)} \times \text{Wt(lb)})/3131] \]

**Carboplatin AUC**

- **Calvert**
  
  \[ \text{Total Dose (mg)} = (\text{target AUC}) \times (\text{GFR} + 25) \]
Role of pharmacokinetics and/or pharmacogenetics

Recommendation # 6.1

• Insufficient pharmacokinetic (PK) data to reject weight-based dosing strategy for cytotoxic chemotherapy for this population

• Further research recommended on role of PK and pharmacogenetic factors

• Paucity of information on the influence of obesity on the PK of most anticancer drugs, especially from properly powered trials
Patient and Clinician Communication

• Provider explanation to patients may be appropriate and/or required
  ➢ If higher doses needed for effectiveness
  ➢ If non-weight-based dosing potentially suboptimal
  ➢ To provide reassurance – increased toxicities not expected and providers will monitor
  ➢ If initial dose suboptimal, clinician can increase to weight-based dose as long as patients can tolerate. Encourage patient to monitor effects of dose changes.
  ➢ To discuss potential cost implications

• Communicate about weight-based dose with patients’ other health care providers (including nurses and pharmacists)
Health Disparities

• Higher rates of obesity among Blacks/African Americans, Hispanics/Latinos, and people of lower socioeconomic status (SES)

• Increased likelihood that patients from these populations receive reduced doses and poorer outcomes

• Black women/African American and women with lower SES with breast cancer may reap the greatest benefits from a change in the common practice of dose limitations in obese patients to full weight-based dosing
Limitations of the literature

- Limited # RCTs addressing issue
- Majority of the studies included in this Guideline are well-done retrospective analyses of randomized trials and comparative observational studies
- The majority of studies were on breast, ovarian, colon, and lung cancer
- This guideline does not address dosing for novel targeted agents
- No RCTs comparing full weight-based chemotherapy dose selection and non-full weight-based dose selection
- RCTs may not adequately address effectiveness in broad, unselected populations with cancer with major comorbidities
Future Directions

• Future research needed:
  ➢ Rigorous systematic review of data from a series of patients enrolled in cooperative group trials – examining data on all patients (with and without co-morbid conditions) who are defined as obese
  ➢ A priori and high-quality methods needed for analysis of body composition and toxicities
  ➢ Prospective pharmacokinetic/pharmacodynamic analysis
The Bottom Line

• *Intervention*
  - Recommendations for appropriate chemotherapy dosing for obese adult patients with cancer

• *Target Audience*
  - Medical Oncologists, Pharmacists, Oncology Nurses

• *Key Recommendations*
  - Panel recommends that full weight-based chemotherapy doses be used in the treatment of the obese patient with cancer, particularly when the goal of treatment is cure.
  - Clinicians should respond to all treatment-related toxicities in obese patients with cancer in the same ways they do for non-obese patients.
The Bottom Line, cont’d

• **Key Recommendations, cont’d:**
  - If a dose reduction is employed in response to toxicity, consideration should be given to the resumption of full weight-based doses for subsequent cycles, especially if a possible cause for the toxicity (e.g. impaired renal, hepatic function) has been resolved. There is no evidence to support the need for greater dose reductions for obese patients compared to non-obese patients.
  - The use of fixed dose cytotoxic chemotherapy is rarely justified (except for a few select agents).

• **Methods**
  - Systematic review of medical literature and analysis of the medical literature by the Update Committee of an Expert Panel
## Guideline Methodology: Panel Members

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Affiliation/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer J. Griggs, MD, MPH, Co-Chair</td>
<td>University of Michigan, Department of Medicine, Division of Hematology/Oncology</td>
</tr>
<tr>
<td>Gary H. Lyman, MD, MPH, FRCP, FASCO, Co-Chair</td>
<td>Duke University and the Duke Cancer Institute</td>
</tr>
<tr>
<td>Holly Anderson</td>
<td>Patient Representative, Breast Cancer Coalition of Rochester</td>
</tr>
<tr>
<td>Edward P. Balaban, DO</td>
<td>University of Pittsburgh Cancer Centers Network, Pittsburgh, PA</td>
</tr>
<tr>
<td>James J. Dignam, PhD</td>
<td>University of Chicago Department of Health Studies</td>
</tr>
<tr>
<td>Willian M. Hryniuk, MD</td>
<td>CarePath</td>
</tr>
<tr>
<td>Vicki A. Morrison, MD</td>
<td>Veterans Affairs Medical Center</td>
</tr>
<tr>
<td>T. May Pini, MD, MPH</td>
<td>Medical Oncology, Houston, TX</td>
</tr>
</tbody>
</table>
### Guideline Methodology: Panel Members, cont’d

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Affiliation/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gary L. Rosner, ScD</td>
<td>Johns Hopkins University, Division of Oncology Biostatistics and Bioinformatics</td>
</tr>
<tr>
<td>Carolyn D. Runowicz, MD</td>
<td>Florida International University</td>
</tr>
<tr>
<td>Michelle Shayne, MD</td>
<td>University of Rochester Medical Center</td>
</tr>
<tr>
<td>Alex Sparreboom, PhD</td>
<td>St. Jude Children’s Research Hospital</td>
</tr>
<tr>
<td>Lara E. Sucheston, PhD</td>
<td>Roswell Park Cancer Institute, Cancer Prevention and Control</td>
</tr>
</tbody>
</table>
Additional ASCO Resources

• The guideline (executive summary) is available at [http://jco.ascopubs.org](http://jco.ascopubs.org)

• 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)
This practice tool for physicians is a summary slide set derived from an ASCO® practice guideline. The practice guideline and this presentation are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This presentation does not recommend any particular product or course of medical treatment. Use of the practice guideline and this resource is voluntary. The full practice guideline and additional information are available at http://www.asco.org/guidelines/wbd. Copyright © 2012 by American Society of Clinical Oncology®. All rights reserved.