Introduction to Cancer
Chemotherapy and Pharmacology

By
Dr. Magdy Saber
Prof. of Medical Oncology,
NCI, Cairo University
Learning Objectives

After completing this program the participant should be able to

- Identify consideration important in dosing chemotherapeutic agents in older patients with cancer
- Describe chemotherapy related toxicities that are more common and/or debilitating in older patients with cancer
- Identify precautions to be taken to ameliorate these toxicities
Chemotherapeutic agents in older patients with cancer: Special consideration

- Anticancer Drugs
- Other Drugs
- Elderly Patient with Cancer
- Target Effects
- Toxic Effects
- Physiological age
- Co-morbidities
- Drug interactions
- Goal of Treatment
- Potential toxicities

South & East Mediterranean College of Oncology
26 – 28 March 2008
Cairo - Egypt
Cancer and the elderly

- Cancer is a disease of aging
- The big 3 — cardiovascular disease, cancer and stroke — increase with age
- 4 out of 5 persons ≥ 65 years of age have one or more chronic conditions
- 60% of all malignant tumors occur in the age group 65 years and older

Fitness does not mean you can all do the same exercise, does it?

- Vulnerable = reversible problem.
- Frail = non reversible problems.
If an elderly person is started on a new medication and 2 to 3 days later they are taken to the emergency room, suspect a drug reaction.
Organ-specific age-related physiological changes

- Kidneys
- Liver
- Lungs
- GI tract
- Body composition
- Cardiovascular
- Hematological
- Nervous system
- Endocrine
Chemotherapy and The Elderly

What are the true limitations?

• Drug distribution and absorption
• Drug interactions
• Renal function
• Liver function
• Marrow reserves
• Neurological
Pharmacokinetics - Overview

- Absorption
  - Routes of drug administration
    - Enteral route
    - Parenteral route
    - Subcutaneous
    - Intramuscular
    - Intravenous
    - Intrathecal
    - Pulmonary route

- Distribution
  - Free drug + protein
  - Unbound drug (pharmacologically active)

- Biotransformation or metabolism
  - Lipid soluble
  - Water soluble

- Excretion
  - Unchanged drug

- Blood vessel
  - Capillary membrane
  - Drug-protein complex
    - Bound drug - pharmacologically inactive

- Target site of action: receptors, etc.
Factors that may affect GIT absorption

- Decreased gastric acid secretion
- Decreased emptying time
- Decreased gastrointestinal tract motility
- Decreased splanchnic blood flow
- Decreased absorption surface
- Concomitant medication, e.g., H₂ blockers, antacids, calcium
- Compliance
Distribution of anticancer agents

The volume of distribution of drugs is a function of **body composition** and the concentration of circulating **plasma proteins** such as serum albumin and **red blood cell** concentration.

- **Fat content** doubles in the elderly from 15% to 30% of body weight.
- **Intracellular water** decreases to 33% in the average 75-year-old compared with 42% in the average 25-year-old.
- This results in a decrease in volume of distribution of more polar drugs, while that of the lipid soluble drugs increases. This can lead to a lower peak concentration and prolonged terminal half.
Distribution of anticancer agents

- Plasma albumin concentration decreases as individual ages (may decrease by 15% to 20% or more, especially with chronic illness, malnutrition, and frailty).
- There is often a reduction of red blood cell concentration.
- Anemia can be particularly relevant for treatment with anthracyclines, taxanes, and epipodophyllotoxins that are heavily bound to red blood cells.
- Other medications may displace protein bound drugs.
Hepatic Metabolism

• Reduced liver size
• Reduced liver flow (at a rate of 0.3% to 1.5% per year after age 25)
• Age related changes in P450 (CYP) microsomal systems (declines by 32% after the age of 70 years).
• Polypharmacy:
  o P450 inducers: sex steroids, phenobarbital
  o P450 inhibitors: cimetidine, grapefruit juice.
• Genetic variability accounts for differing levels of enzyme activity that may lead to clinically important pharmacodynamic differences
## Chemotherapy & P450 metabolism

<table>
<thead>
<tr>
<th>Agent</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2B6</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (+2C8)</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Etoposide(+2E1)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>(x)</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>VLB/VCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

- Phase 2 reactions appear unaffected by age.

<table>
<thead>
<tr>
<th></th>
<th>Median number of potential drug interaction and toxicity per patient</th>
<th>Number interacting with P450</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 (0-17)</td>
<td>2 (0-8)</td>
</tr>
</tbody>
</table>

Extermann et al. ASCO 2003
Dose reduction in hepatic dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adriamycin</td>
<td>50%</td>
<td>75%</td>
<td>Omit</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>25%</td>
<td>50%</td>
<td>Omit</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Omit</td>
<td>Omit</td>
<td>Omit</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epipodophyllotoxins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic alkaloid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0%</td>
<td>25%</td>
<td>Omit</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0%</td>
<td>5%</td>
<td>Omit</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>0%</td>
<td>0%</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Mild: bil. 1.5-3%; SGOT: 60-180. Moderate bil. 3.1-5%; SGOT: >180. Severe: bil. > 5%
Excretion of Drugs

- A decline in glomerular filtration rate (GFR) is one of the most predictable changes associated with age (1ml per minute for every year over 40 years of age).
- Additional effects of comorbid conditions on renal function

The relationship between serum creatinine and GFR

Age and GFR
Creatinine clearance calculation

Formulas for calculation of CrCl from SCr

<table>
<thead>
<tr>
<th>Method</th>
<th>Formula for renal clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>Estimated CrCl (ml/min) = [\frac{(140 - \text{age}) \times \text{weight}}{[72 \times \text{SCr (mg/dl)}^2]} ] (× 0.85 if female)</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>Estimated CrCl (ml/min/1.73 m²) = [\frac{[98 - (0.8 \times (\text{age} - 20))] - [1 - (\text{sex} \times 0.1)]}{\text{SCr (mg/dl)}} ] if sex = 0 if male and 1 if female to give result in ml/min × BSA/1.73</td>
</tr>
<tr>
<td>Wright</td>
<td>Estimated CrCl (ml/min) = [\frac{[6550 - (38.8 \times \text{age})]}{[1 - (0.168 \times \text{sex})]} ] × BSA (m²)/SCr (µmol/l); sex = 0 if male and 1 if female</td>
</tr>
<tr>
<td>Martin</td>
<td>Estimated CrCl (ml/min) = [\frac{[163 \times \text{ABW (kg)} \times (1 - 0.00496 \times \text{age}) \times (1 - 0.252 \times \text{sex})]}{\text{SCr (µmol/l)}} ] if sex = 0 if male and 1 if female</td>
</tr>
<tr>
<td>MDRD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Estimated CrCl (ml/min/1.73 m²) = [\frac{[170 \times \text{SCr (mg/dl)}^{-0.999} \times \text{[age (years)]^{-0.176} \times [0.762 if female] \times [1.18 if African American]}}{\text{[BUN (mg/dl)]^{-0.170} \times [albumin (g/dl)]^{-0.318}}] \text{to give result in ml/min × BSA/1.73} ]</td>
</tr>
<tr>
<td>aMDRD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Estimated CrCl (ml/min/1.73 m²) = [\frac{[186 \times \text{SCr (mg/dl)}^{-1.154} \times \text{[age (years)]^{-0.208} \times [0.742 if female] \times [1.21 if African American]}}{\text{[BUN (mg/dl)]^{-0.170} \times [albumin (g/dl)]^{-0.318}}] \text{to give result in ml/min × BSA/1.73} ]</td>
</tr>
</tbody>
</table>

<sup>a</sup>SCr µmol/l = SCr mg/dl × 88.4.

<sup>b</sup>SCr measured by Jaffé method. If more standardized SCr measurements are used such as peroxidase antiperoxidase, which have recently replaced Jaffé in many institutions, then SCr should be divided by a factor of 0.95 [41, 42].

CrCl, creatinine clearance; SCr, serum creatinine; BSA, body surface area; ABW, actual body weight; BUN, blood urea nitrogen.
Creatinine clearance calculation

- Cockcroft-Gault and Jellife equations are less accurate in the elderly and in patients with severe renal failure or decreased muscle mass.
- The Wright formula is more accurate than the Cockcroft/Gault formula in patients with a glomerular filtration rate of >50\(^1\)
- The MDRD (modification of diet in renal disease) formula is more accurate than other formulas in patients with chronic renal disease. This formula takes into account age, sex, ethnicity, serum creatinine, blood urea nitrogen, and albumin\(^2\)

1`Marx et al, 2004;  
2`Levev et al, 1999; Lichman et al, 2007
**Dose reductions in renal dysfunctions based on CrCl (ml/min.)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>30-60</th>
<th>10-30</th>
<th>&lt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>50%</td>
<td>Omit</td>
<td>Omit</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>20%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0%</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>25%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>50%</td>
<td>Omit</td>
<td>Omit</td>
</tr>
<tr>
<td>Nitrosureas</td>
<td>Omit</td>
<td>Omit</td>
<td>Omit</td>
</tr>
</tbody>
</table>
Influence of age on toxicity of anticancer drugs

• Is Toxicity in older patients = Toxicity in younger patients?

• Concerns:
  - Performance status
  - Concomitant diseases

• Most evaluations and reviews of SIOG Taskforce state that fit older patients without significant co-morbidity and without significant functional impairment should be treated the same as younger patients.
Common Toxicities in Older Persons

- Haematological toxicity: Myelosuppression
- Cardiac toxicities: Cardiomyopathy
- GIT toxicity: Mucositis
- Neurotoxicity
Haematological toxicity/ Myelosuppression

- Reduced haematopoietic reserve capacity:
  - Decreased growth factor secretion
  - Decreased proliferative response to growth factors

Potential solutions to a decreased haematopoietic reserve

- Dose adjustment
- Haematopoietic growth factors:
  - G CSF
  - GM CSF
  - Erythropoietin
  - Thrombopoietic drugs
Cardiotoxicity/Cardiomyopathy

• Risk factors for cardiotoxicity
  - Previous radiotherapy to chest wall
  - Pre existing cardiac disease
  - Age over 65 years

• Culprits
  - Anthracyclines/Anthracenedione
  - Trastuzumab
  - 5-Flourouracil
  - Taxanes
## Cytotoxic drugs that cause Cardiotoxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute-subacute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Endoxan</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5-FU/ VCR/ VLB</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>MTX</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>
# Doxorubicin-related Cardiotoxicity

<table>
<thead>
<tr>
<th>Cumulative dose (mg/m²)</th>
<th>Probability of Heart Failure (%)</th>
<th>Q week</th>
<th>Q 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40-59y</td>
<td>&gt;60 y</td>
</tr>
<tr>
<td>250</td>
<td></td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>300</td>
<td></td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>400</td>
<td></td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>500</td>
<td></td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>600</td>
<td></td>
<td>3.9</td>
<td>6.1</td>
</tr>
<tr>
<td>700</td>
<td></td>
<td>8.7</td>
<td>13.2</td>
</tr>
</tbody>
</table>

Recommendation for safely delivering anthracycline to older patients

- Cytoprotective agents e.g. dexrazoxane (ICRF-187).
- Alternative schedules
  - Continuous infusion
  - Weekly administration
- Use of less cardiotoxic agents
  - Mitoxantrone
  - Epirubicin
  - Liposomal doxorubicin
- Monitor LVEF and clinical symptoms
Cardiotoxicity of 5-fluorouracil

- May cause vascular smooth muscle constriction
- 1.6% incidence of symptomatic cardiac toxicity
- Increase in asymptomatic ST changes from 24% to 68%
- Risk factors:
  - Pre-existing cardiac disease
  - Continuous infusion

GIT Toxicity of Chemotherapy

- Nausea and Vomiting
  - Anticipatory
  - Acute
  - Delayed
- Mucositis
- Diarrhea
Prevention of Acute Emesis

• Single dose of one of the following 5-HT3 receptor antagonists:
  - Dolasetron 100mg PO/IV or 1.8mg/kg IV or
  - Granisetron 0.01mg IV or
  - Ondansetron 0.15mg/kg IV

• Plus:
  - Dexamethasone 20mg IV or
  - Methylprednisolone 40 to 125mg PO or IV
Prevention of Delayed Emesis

Dexamethasone 8mg PO bid x3-4days

Metoclopramide 30-40 mg PO bid- qid x 2-4days

+ or

One of the 5-HT3 receptor antagonists:
Dolasetron 100mg PO/IV or 1.8mg/kg IV x 2-3 days
Granisetron 2mg PO, 1mg IV or 0.01mg/kg IV x 2-3 days
Ondansetron 8mg PO bid-tid, 8mg IV or 0.15mg/kg IV 2-3 days
GIT mucosal toxicity of chemotherapy

- Metaanalysis of 3,351 patients enrolled in phase III trials of colon cancer
  - No age related difference in the likelihood of mucositis with 5-FU
- Review of prospective colorectal cancer database
  - Severe mucositis more frequent in patient over 70 years

GIT mucosal toxicity of chemotherapy (cont.)

- Metastatic colon cancer
  - 5-FU 600mg/m2 with LV resulted in 11 toxic deaths (10 of them were persons aged > 63 years)

- Adjuvant breast cancer
  - Classic CMF in women aged 65 years or above had higher grades of toxicities

Amelioration of GI mucosal toxicity

- Oral cryotherapy and oral rinses
- Dose and schedule selection
- Rapid correction of dehydration and management of symptoms
- Treatment of secondary infection
Neurotoxicity

Peripheral neuropathy
- Vinca alkaloid
- Epipodophyllotoxins
- Synthetic alkaloid
- Taxanes
- Cisplatin
- oxaloplatin

Central toxicity
- Cytarabine
- 5-FU
- Nitrosureas
- Dacarbazine
- Fludarabine
- Ifosfamide
- interferon
Summary

• Toxicity may be more severe and/or debilitating in the older person
  - Myelosuppression
  - GI toxicity
  - Cardiotoxicity
  - Neurotoxicity

• Determining the patient- and regimen-specific factors that predict the risk for toxic effects of chemotherapy would be clinically relevant.

• Will the patient die of or with cancer?
  - Frailty
  - Co-morbidity

• Morbidity of therapy > morbidity of cancer?

• Will dependency be increased?
Summary

• To screen cancer patients likely to receive chemotherapy:
  - No major organ failure (few comorbidities).
  - Good performance status (no dependency).
  - Able to follow experimental treatment (no dementia).
  - Without drug interaction (no polypharmacy).

• Developing new chemotherapy regimens with similar efficacy but less toxicity in elderly patients should be a priority for future research.

Neither «frail», nor «too sick» patients
Thank you