Principle and clinical pharmacology of chemotherapy

Vichien Srimuninnimit, MD
Medical Oncology Division
Faculty of Medicine, Siriraj Hospital
Content

- Principle of chemotherapy
- Pharmacology of chemotherapy
- Dose calculation
- Tumor assessment
Tumor Growth Curve: Sigmoid-shaped curve
Gompertzian Tumor Growth

- The lag phase
  - growth by host factors
- The Log phase
  - growth by angiogenesis
  - High growth fraction (ratio of dividing cell to total cells)
- The plateau phase
  - Low growth fraction
  - High death rate of cells

- The larger the tumor mass, the greater the percentage of non-dividing and dying cells and the longer it takes for the average cell to divide.

Cancer Treatment Options

- Surgery: before 1955
- Radiotherapy: 1955~1965
- Chemotherapy: after 1965
- Endocrine therapy
- Targeted therapy
- Immunotherapy
The Cell Kill Hypothesis

• Each chemo cycle kills 90% of malignant cells
  • 1000 >> 100 >> 10 >> 1
• Tumor burden will never reach zero
• Assumes once < $10^5$, immune system eliminates micrometastasis

Assumptions

• Lack of metastatic disease (i.e. stage doesn’t matter)
• All cells (and all tumors) have equal sensitivity to chemotherapy and equal % of dividing cells
• All drugs (single agent vs. combinations) kill the same fixed percentage
• Role of chemotherapy resistance?
Goldie-Coldman Hypothesis

- Tumors are heterogeneous

- The larger the tumor, the more cycles of division, the greater the mutations, the more heterogeneous the tumor

- Chemotherapy eliminates the bulk of the tumor initially (chemo-sensitive cell lines) but in relapse the tumor contains the MDR clone
The Cell Cycle

- Malignant cells go through normal mitosis, but synthesize DNA and divide at a faster rate.
- Most chemo drugs exert antineoplastic effects during DNA synthesis (S-phase) or mitosis:
  - Cell Cycle Specific (CCS) drugs
- Other chemo drugs sterilize tumor cells whether they are cycling or resting in the G0 compartment:
  - Cell Cycle Non-Specific (CCNS)
Cell Cycle

Stages of the cell cycle:
- G0 - quiescent cells
- G1 - Gap phase 1
- S - DNA synthesis
- G2 - Gap phase 2
- M - mitosis

Start of cycle
- Cell enlarges and makes new proteins
- Cell rests
- G0
- Diff

Restriction point, cell decides whether to commit itself to the complete cell cycle

Cell prepares to divide
- Cell divides (mitosis)

Cell replicates its DNA
- S

M - mitosis
Categories of chemotherapy

• **Phase nonspecific**
  – **Cycle-nonspecific drugs**: killing nondividing cells (e.g., steroid hormones, antitumor antibiotics except bleomycin)
  – **Cycle-specific, phase-nonspecific drugs**: alkylating agents
  – **Pharmacokinetics**: linear dose-response curve. The greater the amount of drug administered, the greater the fraction of cell killed

• **Phase specific**
  – **Cycle-specific, phase-specific drugs**
  – **Pharmacokinetics**: their effect is a function of both time and concentration
Cancer Chemotherapeutic Agents

1. **Covalent DNA-binding drugs: cycle-specific, phase-non specific**
   - Alkylation agents: Cyclophosphamide, ifosfamide
   - Platinum: Cisplatin, carboplatin, oxaliplatin

2. **Antimetabolites: S-phase**
   - Methotrexate, pemetrexed, 5-Fluorouracil, capecitabine, TS-one
   - Gemcitabine

3. **Antitumor antibiotics: cycle-nonspecific**
   - Doxorubicin, epirubicin, liposomal doxorubicin, mitoxantrone
   - Bleomycin (G2 phase), mitomycin-C, actinomycin D

4. **Mitotic spindle agents: M phase**
   - Taxanes: paclitaxel, docetaxel, nab-paclitaxel, cabazitaxel
   - Vinca alkaloids: vincristine, vinblastine, vinorelbine
   - Eribulin

5. **Topoisomerase inhibitors: S phase**
   - Topoisomerase-1 inhibitors: irinotecan, topotecan
   - Topoisomerase-2 inhibitors: etoposide
MoA of Ankylators

Alkylating Agents

Form highly reactive carbonium ion

Transfer alkyl groups to nucleophilic sites on DNA bases

Results in

Cross linkage
Abnormal base pairing
DNA strand breakage

Alkylation also damages RNA and proteins

↓ cell proliferation
Cyclophosphamide

Availability:
Oral use: 50 mg/tab; IV use: 100, 200, 500 mg-vials

Administration:
Diluted in D5W or NSS to 20 mg/ml infused over 15 to 60 mins.; rapid infusion (< 5-10 min) may cause light headedness, nausea, perioral numbness

Indication:
wide variety of cancer types

Toxicities: myelosuppression, N&V, hemorrhagic cystitis, gonadal failure, alopecia, SIADH,
Ifosfamide

Availability: 1 gm-vial; mesna: 200, 400 mg-ampules
Administration: Patients should receive at least 2 L per 24 hr of supplement hydration. Ifosfamide is normally dilute in D5W or NSS 50 mg/ml IV infused over 30 to 60 minutes for 3-5 days
Mesna dose of 20% of the ifosfamide dose is given as a loading dose followed by 4 and 8 hours to protect hemorrhagic cystitis.
Indication: refractory lymphoma, relapsed germ cell tumor, bone and soft tissue sarcoma,
Toxicities: myelosuppression, N&V, alopecia, renal toxicity, hemorrhagic cystitis, encephalopathy (high doses)
DNA Binding

- Cisplatin binds to DNA and causes a critical structural change in the DNA – a bend of 45 degrees.
Cisplatin

Availability: 10, 50, 100 mg-vials
Administration: diluted in NSS or D5W infused over 1-2 hrs.
Prehydration and force diuresis (mannitol) for cisplatin administration followed by additional saline infusion
Indication: germ cell tumor, lung cancer, osteosarcoma, Squamous cell carcinoma (head and neck, esophagus, skin, cervix, etc), ovarian, endometrial, gastric, bladder cancer, neuroblastoma.
Toxicities: severe N&V, nephrotoxicity, ototoxicity, peripheral neuropathy, mild myelosuppression
Cisplatin

• Toxicities:

• Dose limiting toxicities:

  • Cumulative renal insufficiency

  • Peripheral sensory neuropathy (after 200 mg/m2)

  • Ototoxicity with tinnitus and high frequency hearing loss

• Common: severe nausea and vomiting (both acute and delayed), hypokalemia, hypomagnesemia and mild myelosuppression
Cisplatin

• Check renal function and electrolyte, K+, Mg before given cisplatin

• Avoid using cisplatin when CrCl< 40 ml/min

• Antiemetics: prophylactic antiemetics as ondansetron, dexamethasone and olanzapine or aprepitant

• Hydration and diuresis (furosemide or mannitol): to increase urine output before cisplatin administration and continue hydration (IV or PO) for 24 hours after the drug is given. IV fluid are supplemented with KCL and MgSO4

• May administer 12.5-50 g mannitol/L

• Standard dilution: dose/250-1000 mL NS, D5W/NS or D5/1/2NS rate varied from a 15-120 min infusion
Carboplatin

Availability: 50, 150, 450 mg-vials
Administration: Can be diluted to 0.5 mg/ml with D5W or 0.9% NSS IV infused over 15 to 60 minutes,
No need hydration before administration
Indication: Same activity as cisplatin (but less efficacy in head and neck and esophagus)
Toxicities; myelosuppression (thrombocytopenia), moderate N&V, less neurotoxicity, nephrotoxicity, ototoxicity than cisplatin. Can cause Anaphylaxis: Type I hypersensitivity (IgE mediated): Increased incidence with increased exposure (> 6 cycles)
Carboplatin: Dosing

- GFR and platelet nadir closely related due to almost exclusive renal elimination of carboplatin

- Dose (mg) = AUC x (GFR + 25)

- AUC = area under the concentration vs. time curve

- Usual target 5-6; 4 if debilitated patient

- GFR = glomerular filtration rate (calculated creatinine clearance by Cockcroft-Gault equation used)

- GFR MUST BE CAPPED AT 125ml/min!

- Controversies: Ideal vs. actual vs. adjusted body weight? – see service specific policies

- Creatinine rounding rules

  - if creatinine < 0.8 mg/dL, do you round up to 0.8 mg/dL?

Oxaliplatin

Availability: 50, 100, 200 mg-vial
Administration: diluted in **D5W 250-500 ml** infused over 2 hours. Do not use NSS. No prehydration
Indication: Colorectal cancer, pancreatic and gastric cancer
Toxicities: peripheral neuropathy, moderate N&V, oropharyngeal dysesthesia, no nephrotoxicity, no ototoxicity, rare myelosuppression

Neuropathy: 1. Acute dysesthesias: in the hands, feet, perioral area, or throat develop within hours or up to 2 days after dosing, precipitated by exposure to cold; usually resolves within 2 weeks and may be ameliorated by prolonging the infusion to 6 hours
2. Chronic: persistent peripheral sensory neuropathy
Antimetabolites

- **S-phase specific**

- Resemble naturally occurring nuclear structural components ("metabolites")

- Examples
  - Antifolates: methotrexate, pemetrexed
  - Purine analogs: fludarabine
  - Pyrimidine analogs: 5-FU, gemcitabine
Methotrexate

- Methotrexate potently inhibits Dihydrofolate reductase (DHFR).

- This leads to decreased production of compounds adenine, guanine and thymidine and the amino acids methionine and serine, depletion of thymidine.

- Finally depressed DNA, RNA, and protein synthesis and, ultimately, to cell death.

\[
\begin{align*}
\text{FH}_2 &= \text{dihydrofolate}; \\
\text{FH}_4 &= \text{tetrahydrofolate}; \\
\text{dTMP} &= \text{deoxythymidine monophosphate}; \\
\text{dUMP} &= \text{deoxyuridine mono phosphate}.
\end{align*}
\]
Methotrexate

Availability: oral use: 2.5 mg/tab
  IV use: 5 mg, 50 mg, 1 gm-vials
Administration: may diluted in D5W and NSS. IV bolus, intrathecal routes (preservative free), High-dose methotrexate with leucovorin
Indication: head and neck, skin, bladder, breast cancer, osteosarcoma, choriocarcinoma, Non-Hodgkin’s lymphoma, ALL, carcinomatosis meningitis, mycosis fungoides
Toxicities: myelosuppression, mucositis, diarrhea, N&V, renal toxicity (high dose), allergic pneumonitis
Pemetrexed (multitargeted antifolate)

Spectrum of Activity of Pemetrexed vs. MTX

<table>
<thead>
<tr>
<th>Agent</th>
<th>TS</th>
<th>DHFR</th>
<th>GARFT</th>
<th>AICARFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*TS = thymidylate synthase; DHFR = dihydrofolate reductase; GARFT = glycinamide ribonucleotide formyltransferase; AICARFT = aminooimidazole carboxamide ribonucleotide formyltransferase
Pemetrexed

Availability: 500 mg-vial

Administration: diluted in NSS 100 ml IV drip over 10 minutes
Patient should receive folic acid (0.4-1 mg) daily and vitamin B12 1000 microgram IM supplement repeat every 3 cycles
Dexamethasone: 4 mg PO bid on the day before, day of, and day after pemetrexed administration to help prevent skin rash

Indication: non-small cell lung cancer (nonsquamous cell carcinoma), mesothelioma

Toxicities: myelosuppression, mild to moderate N&V, mucositis, skin rash, diarrhea
Caution: use only when CrCl $\geq$ 45 m/min
5-FU Anabolism

- 5-FU is converted to FUdR by thymidine phosphorylase
- Phosphorylation of FUdR by thymidine kinase results in formation of the active 5-FU metabolite
  - 5-fluoro-2’-deoxyuridine monophosphate (FdUMP)
- In presence of reduced folate cofactor, 5,10 methylenetetrahydrofolate, FdUMP forms a stable covalent complex with thymidylate synthase (TS)
- Inhibition of TS leads to depletion of dTTP, interfering with DNA biosynthesis and repair
5-Fluorouracil

• MOA: depends on rate of infusion
  • Continuous: inhibition of thymidylate synthase (TS)
  • Thymidine deficiency = inhibition of DNA synthesis
  • Leucovorin enhances stability of the FdUMP-TS complex
  • Bolus: false base integration into RNA
  • Also directly integrated into DNA, contribution to cell kill is unclear

• Administration: IV, topical
  • Clearance: dihydropyrimidine dehydrogenase (DPD)
  • Pharmacogenomics: DPD deficiency
5-Fluorouracil

Availability: 500, 1000 mg-vials
Administration: IV bolus, continuous infusion, protracted infusion. May diluted in D5W or NSS
Indication: Colorectal, breast, gastric, pancreas, esophagus cervical, head and neck, skin, vulva cancer
Toxicities: myelosuppression, mild N&V, stomatitis, mucositis, diarrhea, hyperpigmentation, skin rash, phlebitis, hand-foot syndrome, mild alopecia, cerebellar ataxia, chest pain (coronary spasm)
Capecitabine

Availability: 500 mg/tab.
Administration: orally in 2 divided doses at the end of a meal. Use 14 days every 3 weeks
Indication: breast, colon, gastric
Toxicities: mild myelosuppression, stomatitis, diarrhea, hyperpigmentation, hand-foot syndrome
Dose modification:
  CrCl 30-50 ml/min: reduce dose by 25%
  CrCl <30 ml/min: contraindicated
Warning: may increase the anticoagulant effects of warfarin
Gemcitabine

Availability: 200 mg, 1000 mg-vials
Administration: diluted in NSS to < 40 mg/ml infused over 30 minutes
Indication: non-small cell lung cancer, breast, pancreas, bladder, nasopharynx, ovary, soft tissue sarcoma, bile duct
Toxicities: myelosuppression, mild to moderate N&V, mild alopecia, skin rash, fever, elevated LFT
Anti-tumor Antibiotics
Anti-tumor Antibiotics

- **Isolated from soil Streptomyces species**

- **Examples**
  - Anthracyclines: Doxorubicin, epirubicin
  - Anthracenedione (mitoxantrone)
  - Bleomycin
  - Actinomycin-D (Dactinomycin, not discussed)
  - Mitomycin-C
Anthracyclines

- **Intercalating topoisomerase inhibitors**
- Topoisomerase II inhibition (major)
- DNA intercalation (minor)
- Free radical formation (minor)

All are P-glycoprotein substrates

[Chemical structures of doxorubicin, daunorubicin, epirubicin, and idarubicin]
Doxorubicin

Availability: 10 mg and 50 mg-vials
Administration: diluted in D5W or NSS and bolus injection through a freely running intravenous infusion
Indication: a large variety of tumors
Toxicities: myelosuppression, alopecia, mucositis, vesicant agents, N&V, congestive cardiomyopathy (cumulative dose 550 mg/m2 or 450 mg/m2 in hypertension patient)

Caution:
Total bilirubin: 1.2-3.0 mg/dL reduction of dose by 50%
3-5 mg/dL reduction of dose by 75%

Dexrazoxane is a cardioprotectant may use when dose > 300 mg/m2
Epirubicin

Availability: 10 mg and 50 mg-vials

Administration: diluted in D5W or NSS and bolus injection through a freely running intravenous infusion

Indication: Same as doxorubicin

Toxicities: Same as doxorubicin but less myelosuppression, and cardiomyopathy (cumulative dose 800-1000 mg/m2)
Pegylated liposomal doxorubicin

Availability: 20 mg-vial
Administration: diluted in D5W 250 ml (for <90 mg) and 500 mL (for >90 mg) infuse over 60 mins.
Do not use other IV fluids. Do not bolus infusion

Indication: AIDS-related Kaposi’s sarcoma, breast, ovarian

Toxicities: myelosuppression, N&V, acute infusion reaction (flushing, dyspnea, facial swelling, back pain, chest pain, hypotension), hyperpigmentation, mucositis, hand-foot syndrome, less alopecia, not vesicant agent. 
less cardiomyopathy than doxorubicin (cumulative dose should be less than 400 mg/m2
Mitoxantrone

Availability: 10 mg, 20 mg-vial
Administration: diluted in at least 50 ml of D5W or NSS
Standard dilution: dose/100 mL D5W or NSS infuse
over 15-30 minutes
Indication: Acute leukemia, lymphoma, prostate cancer.
Toxicities: Same as doxorubicin but less alopecia, N&V,
and cardiomyopathy (cumulative dose 140 mg/m2),
not vesicant agent
Bleomycin

• Bleomycin-Fe complex reduces O2 to reactive oxygen species

• DNA single strand breaks (major)

• DNA intercalation (minor)

• Cell cycle specific: G2 & M phase

• Doses expressed in units of drug activity

• IV, IM, subcutaneous, intralesional, pleural administration (sclerosing agent)
Bleomycin: Side effects

- Tissues lacking bleomycin hydrolase
- Skin hyperpigmentation, keratosis, desquamation, ulceration
- Nail changes
- Pulmonary (dose related)
- Hypersensitivity, flu-like symptoms
- Minimal benefit of test doses
- Acute hyperthermia followed by cardiac arrest (1%)
- Not myelosuppressive!
Bleomycin

Availability: 15 unit-vial
Administration: dilute in 10 mL of NSS intravenous slowly over 10 minutes or longer. Lymphoma patients should be tested with 2 units for the first 2 doses.
Indication: germ cell tumors, squamous cell carcinoma, lymphoma, malignant pleural effusion (medical pleurodesis)
Toxicities: rare myelosuppression, fever with chill, anaphylaxis, hyperpigmentation, mucositis, pulmonary fibrosis (cumulative dose 400 U.)
Dose modification: CrCl: >50 mL/min no dose adjustment
  40-50 mL/min 70% of normal dose
  30-40 mL/min 60% of normal dose
  20-30 mL/min 55% of normal dose
  10-20 mL/min 45% of normal dose
  5-10 mL/min 40% of normal dose
Bleomycin Pulmonary Toxicity

• **Most common: interstitial pneumonitis and lung fibrosis**
  
  • Due to low amount of bleomycin hydrolase in the lungs. Often reversible upon drug discontinuation (unless fibrosis present). No proven effective therapy

• Potential risk factor: concurrent use of G-CSF with bleomycin (in ABVD for Hodgkin ‘s Lymphoma)

• G-CSF recruits pulmonary neutrophils which increase free radical induced lung damage (Azoulay E, et al. Crit Care Med 2003.)

## Bleomycin Pulmonary Toxicity

### Table 1—Characteristics of BIP

<table>
<thead>
<tr>
<th>Categories</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms and signs</td>
<td>Nonproductive cough, dyspnea, tachypnea, fever, cyanosis</td>
</tr>
<tr>
<td>Established and probable risk factors</td>
<td>Dose of bleomycin, age of patient, smoking, renal dysfunction, radiotherapy, administration of oxygen, underlying lung disease</td>
</tr>
</tbody>
</table>
Mitomycin C

Availability: 2 mg and 10 mg-vials
Administration: IVPB: dose/100 mL NSS and infuse slowly into the tubing of a freely running intravenous infusion
Indication: non-small cell lung cancer, gastric, anal, breast, liver, pancreas, colon

Toxicities: myelosuppression (delayed and cumulative), mild N&V, mucositis, vesicant agents, microangiopathic hemolytic anemia, pulmonary fibrosis, cardiomyopathy (rare)
Anti-microtubule Agents

Vinca alkaloids, Eribulin prevent microtubule assembly.

Alpha tubulin

Beta tubulin

Taxanes prevent microtubule disassembly.
Vincristine, Vinblastine, Vindesine, Vinorelbine: Inhibition of mitotic spindle formation by binding to tubulin. M-phase of the cell cycle.

Paclitexal: binds to tubulin, promotes microtubule formation and retards disassembly; results in mitotic arrest.
Vincristine

**Availability:** 1 mg, 2 mg-vials

**Administration:** bolus injection through a freely running intravenous infusion

**Indication:** Hodgkin’s and Non Hodgkin’s lymphoma, Wilms’ tumor, Ewing’s sarcoma, neuroblastoma, rhabdomyosarcoma, small cell lung cancer

**Toxicities:** rare myelosuppression, peripheral neuropathy, constipation, vesicant agent, mild alopecia, SIADH

**Dose modification:**
- Renal impairment: no dose adjustment
- Hepatic impairment:
  - if bilirubin 1.5-3 mg/dL  decrease dose 50%
  - 3-5 mg/dL  decrease dose 75%
  - > 5 mg/dL  not recommend
Vinblastine

Availability:  10 mg-vial
Administration:  bolus injection through a freely running intravenous infusion
Indication:  lymphoma, mycosis fungoides, germ cell tumor, non-small cell lung cancer, breast, bladder cancer, Kaposi’s sarcoma, choriocarcinoma
Toxicities:  myelosuppression, mild N&V, mucositis, less peripheral neuropathy, mild alopecia, vesicant agent, SIADH
Dose modification:  Same as vincristine
Vinorelbine

Availability: 10 mg, 50 mg-vials
Administration: diluted in D5W or NSS to 0.5 to 2.0 mg/dl in an intravenous bag slow infuse over 6 to 10 mins. followed by flushing with at least 75-125 ml of fluid
Indication: Hodgkin’s lymphoma, non-small cell lung cancer, breast, ovarian
Toxicities: myelosuppression, mild to moderate peripheral neuropathy, constipation, mild N&V, vesicant agent, phlebitis, mild alopecia
Dose modification: Same as vincristine
Eribulin

Availability: 1 mg-vials
Administration: diluted in NSS 50-100 ml infused over 2-5 minutes. No need for antiemetic drug for the first cycle
Indication: metastatic breast cancer, liposarcoma
Toxicities: myelosuppression, fatigue, alopecia, neuropathy
Dose modification:
   Renal impairment: CrCl 15-49 mL/min  1.1 mg/m2 IV
   Hepatic impairment:
      Mild (Child-Pugh A):  1.1 mg/m2 IV
      Moderate (Child-Pugh B):  0.7 mg/m2 IV
Paclitaxel

Availability: 30 mg, 100 and 300 mg-vials

Administration: diluted in either NSS or D5W to a final concentration of 0.3 to 1.2 mg/ml. Usually infused over 1 to 3 hours. Non-PVC administration set should be used and an in line filter with a microporous membrane not greater than 0.22 microns

Need premedication 30-60 mins before administration:
- diphenhydramine 50 mg IV or PO
- ranitidine 50 mg IV or 150 mg PO and
dexamethasone 20 mg IV (10 mg for 1 hour infusion)

Standard dilution (IVPB):
- dose/500 mL D5W or NSS over 3 hours
- dose/250 mL D5W or NSS over 1 hour
Paclitaxel

Indication: breast, lung, ovarian, endometrial, cervical, head and neck, esophageal, gastric, bladder, AIDS-related Kaposi’s sarcoma

Toxicities: hypersensitivity reaction: flushing, hypotension, bronchospasm, urticarial, diaphoresis, pain or angioedema (usually occur within 2 to 3 minutes after treatment and almost always occur within the first 10 minutes) most occur after the first and second dose, myelosuppression, peripheral neuropathy, myalgia/arthralgia (within 3 days and lasting for 1 week), mild to moderate N&V, alopecia, mucositis, diarrhea, cardiac arrhythmia (bradycardia)
Paclitaxel Dosing and Administration

- **Paclitaxel dosing**
  - Weekly (80mg/m²) over 1 hour vs. q 3 weeks (175mg/m²) over 3 hours
  - Greater efficacy w/weekly vs. q 3 wk but more neuropathy and more patient inconvenience, less myelosuppression

- **IV over 3 hr vs. 24 hr?**
  - 24 hr infusion increases neutropenia and mucositis but decreases hypersensitivity and neuropathy vs. 3 hr infusion

- When administered on the same day as cisplatin or carboplatin, give the paclitaxel FIRST

- Cisplatin and carboplatin impairs paclitaxel clearance 25% = worsened myelosuppression

Nab paclitaxel (Abraxane®)

- Nab = nano-particle albumin bound
- No cremophor = no pre meds
- Enhanced uptake into tumor cells
- Nab-paclitaxel and conventional paclitaxel are NOT interchangeable!
Nab-paclitaxel
(protein-bound paclitaxel)

• Availability: 100 mg-vial
• Administration: diluted in NSS 100-250 ml infused over 30 minutes. Premedication for hypersensitivity reaction is not required. No need for in-line filter.
• Indication: metastatic breast cancer, pancreatic cancer
• Toxicities: myelosuppression, sensory neuropathy, arthralgia/myalgia, alopecia, fatigue
Docetaxel

Availability: 20 mg and 80 mg-vials
Administration: diluted in either NSS or D5W to concentration of 0.3 to 1.2 mg/ml infused over 1 hr. Need premedication with dexamethasone 8 mg po twice daily for 3 days starting 1 day before docetaxel
Indication: breast, lung, head and neck, gastric, mCRPC
Toxicities: myelosuppression, hypersensitivity, fluid retention (edema, weight gain, pleural effusion, ascites), skin rash, nail change, peripheral neuropathy, alopecia, myalgia/arthralgia, stomatitis, diarrhea, mild to moderate N&V
Cabazitaxel

Availability: 60 mg-vial

Administration: diluted in 250 mL PVC-free container of either NSS or D5W infused over 1 hr. Use an in-line filter. Need premedication (diphenhydramine 25 mg IV, dexamethasone 8 mg IV, ranitidine 50 mg IV) 30 minutes before each dose.

Indication: metastatic prostate cancer previously treated with docetaxel regimen.

Toxicities: myelosuppression, diarrhea, fatigue, peripheral neuropathy, alopecia, myalgia/arthralgia, mild to moderate N&V.
**Mechanism of action:** DNA Topoisomerases I and II are essential enzymes for transcription, replication and mitosis. The following drugs are able to inhibit these enzymes.

<table>
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<th>Topoisomerase I inhibitors</th>
<th>Topoisomerase II inhibitors</th>
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<tr>
<td>Irinotecan</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Teniposide</td>
</tr>
</tbody>
</table>
Topoisomerase inhibitors

A. Supertwisting resulting from unwinding of the double helix
- DNA double helix
- Strand separation
- Positive supercoiling

B. Action of Type I DNA topoisomerase
- Nick
- Topoisomerase I
- Topotecan
- Nick sealed

A. Normal catalytic cycle of topoisomerase
- Topoisomerase II
- Double-stranded DNA
- Transient, cleavable complex
- Noncleavable complex

B. Etoposide leads to double-strand breaks in DNA
- Persistent, cleavable complex
- Irreversible double-strand breaks in DNA
Irinotecan or CPT-11

Availability: 40 mg and 100 mg-vials
Administration: diluted in D5W or NSS 250 ml (or to a concentration of 0.12-1.1 mg/ml) infused over 45-90 minutes
Indication: colorectal cancer, lung cancer, gastric
Toxicities: myelosuppression, diarrhea, N&V, constipation, alopecia, acute cholinergic reaction (abdominal cramping, N&V, sweating, flushing, diarrhea)

Active metabolite: SN-28 occur mainly in the liver and was metabolized by enzyme UGT1A1 (UGT1A1*1 is the normal allele)
Pharmacogenomics: homozgyous for UGT1A1*28 allele have reduced UGT1A1 activity and increased risk of grade 4 neutropenia
Irinotecan (CPT-11)

• **Side effects**
  
  • Acute (< 24h) diarrhea due to cholinergic stimulation
    
    • CPT-11: cholinergic agonist + acetylcholinesterase inhibitor
  
    • Treatment: IV atropine 0.25-1mg
  
  • Delayed diarrhea (> 24h): GI mucosal damage
    
    • Treatment: oral antidiarrheal drugs (ex: loperamide)
  
  • Alopecia, myelosuppression (dose limiting)
Topotecan

Availability: 4 mg-vial and 0.25 and 1 mg-capsule

Administration: diluted in D5W or NSS to 0.01-0.5 mg/ml
infuse over 30 minutes for 5 days

Indication: ovarian cancer, small cell lung cancer,

Toxicities: myelosuppression, mild N&V, alopecia, diarrhea
Etoposide or VP-16

Availability: oral: 50 mg-capsule
IV use: 100 mg-vial

Administration: diluted in NSS or D5W to a concentration of 0.2 to 0.4 mg/ml infuse over 30 to 60 minutes to avoid hypotension. Do not bolus infusion

Indication: germ cell tumor, lung cancer, trophoblastic disease, pediatric sarcoma (Ewing’s sarcoma), Kaposi’s sarcoma, Acute leukemia, non-Hodgkin’s lymphoma

Toxicities: myelosuppression, hypotension (rapid infusion), alopecia, mild to moderate N&V, mucositis, peripheral neuropathy (rare)
Body Surface Area Formulae

- **DuBois & DuBois (1916)**
  \[ BSA = 0.20247 \times \text{Ht (m)}^{0.725} \times \text{Wt (kg)}^{0.425} \]

- **Boyd (1935)**
  \[ BSA = 0.0003207 \times \text{Ht (cm)}^{0.3} \times \text{Wt (g)}^{0.7285-0.0188 \times \log(\text{wt})} \]

- **Gehan & George (1970)**
  \[ BSA = 0.0235 \times \text{Ht (cm)}^{0.42246} \times \text{Wt (kg)}^{0.51456} \]

- **Haycock et al. (1978)**
  \[ BSA = 0.024265 \times \text{Ht (cm)}^{0.3964} \times \text{Wt (kg)}^{0.5378} \]

- **Mosteller (1987)**
  \[ BSA = \sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3600}} \]
Different Approaches for Dosing in Obesity

- Various non-evidenced based approaches
  - Actual body weight
  - Ideal body weight (IBW)
  - Adjusted ideal body weight (between actual weight and IBW)
  - Capping BSA @ eg. 2 m²
ASCO Guidelines – Obesity (1)

- 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

Tumor Assessment: RECIST 1.1
What are Target Lesions?

- Measurable lesions
- There are different rules for nodal target lesions and non-nodal target lesions.
What are Target Lesions?

Nodal vs. Non-nodal

Non-nodal target lesions must be:

- ≥ 10 mm long axis when evaluated with CT Scan
- ≥ 20 mm long axis when evaluated with Chest X-ray
- ≥ 10 mm long axis with calipers
What are Target Lesions?

Nodal vs. Non-nodal

Lymph Nodes:

- ≥ 15 mm short axis for target
Disease Definitions

What are Non-target Lesions?

- Pathologic lesions too small to be considered target lesions
- Lesions not qualifying as target lesions due to restrictions on the number of target lesions from a single site or total number of target lesions
- Truly non-measurable lesions
  - Bone lesions
  - Pleural/pericardial effusion and ascites
  - Inflammatory breast disease
  - Lymphangitis cutis/pulmonis
  - Cystic lesions
  - Leptomeningeal disease
Response Definitions

Complete Response (CR)

Disappearance of all non-nodal target lesions
Reduction in short axis of all nodal target and nodal non-target lesions to < 10mm
Disappearance of all non-nodal non-target lesions
Partial Response (PR)

A 30% decrease in the *Sum of Axes of Target Lesions (SATL)* when compared to the *baseline sum* AND

A response of non-PD in non-target lesions
Progressive Disease (PD)

A 20% increase in the \((\text{SATL})\) when compared to the smallest SATL ever reported

AND

A \(\geq\) 5mm increase over that SATL

And/Or

Presence of new lesions*

* Specific requirements discussed later
Response Definitions

Stable Disease (SD)

Criteria for CR, PR or PD are not met

Section 6.0 of the protocol defines the minimum time frame required between the start of treatment and follow-up scan for SD to be reported
should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

**Target Lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the

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**Target lesion restrictions**

2 target lesions per organ

5 target lesions in total

Lesions with longest axes and are suitable for repeated measurements
### Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of measurement criteria.

#### For Patients with Measurable Disease (i.e., Target Disease)

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Best Overall Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD***</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD***/not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD***/not evaluated</td>
<td>No</td>
<td>SD</td>
<td>Documented at least once ≥ 6 weeks from study entry</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>PD**</td>
<td>Yes or No</td>
<td>PD**</td>
<td>No prior SD, PR or CR</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions—Progressive Disease section for further explanation.

**Note:** Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
When not to use chemotherapy

• When facilities are inadequate to evaluate the patient response to therapy and no monitor and manage toxic reactions
• When the patient is not likely to survive longer even if tumor shrinkage could be accomplished
• When the patient is not likely to survive long enough to obtain benefits from the drug (e.g., severely debilitated patients)
• When the patient is asymptomatic with slow-growing, incurable tumors, in which case chemotherapy should be postponed until symptoms require palliation