Pharmacology/Therapeutics II Block IV

2013-14

75. Chemotherapy I: Overview – **Micetich**
76. Chemotherapy II: alkylating Agents – **Micetich**
77. Chemotherapy III: Antibiotics/Anti-tumor Agents - **Micetich**
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CHEMOTHERAPY I: OVERVIEW

Date: April 9, 2014 – 10:30 am

Reading Assignment: Katzung, p. 1097-1100 (antiemetics); pp. 592-595 (myeloid growth factors and megakaryocytic growth factors).

KEY CONCEPTS & LEARNING OBJECTIVES

1. Define the subclinical or latent phase of the growth of a cancer and list the properties that can develop during this period that determine the biology of the cancer and the outcome with treatment.

2. Define the Skipper Hypothesis and the Goldie-Coldman hypothesis and how they relate to outcome after treatment with chemotherapy.

3. List the steps in the metastatic process.

4. List the categories of response to chemotherapy

5. Define the three phases of drug development and state the goals of each of the phases.

6. Define chemotherapy

7. List the constitutional toxicities of chemotherapy

8. List the toxicities of chemotherapy due to the effect of chemotherapy on the normal dividing cells

9. Define myelosuppression

10. List the pharmacologic agents available to ameliorate nausea and emesis, and neutropenia.

11. Define cumulative toxicity

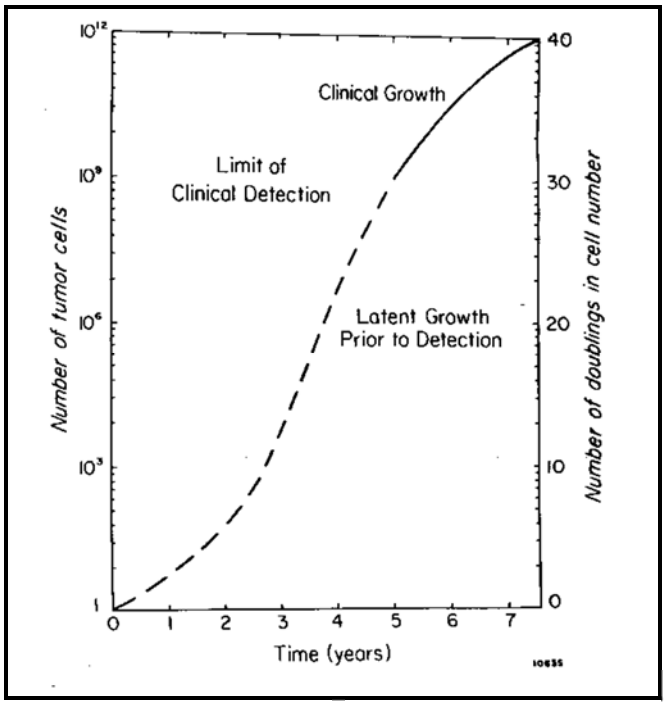
CHEMOTHERAPY I: OVERVIEW

1. **TRANSFORMATION:** Change to the malignant phenotype. Cancer is an accumulation of genetic alterations and is a multi-step process.

2. **CONTINUED CELL DIVISION:** Continued cell division occurs until the cancer becomes clinically detectable.

   a) Phases of the cell cycle: Go, G1, S, G2, M.
   b) Tumor stem cells

3. **SUBCLINICAL OR LATENT PHASE OF THE CANCER:** The **subclinical or latent phase** of the cancer is the time from the inception of a cancer (transformation of a single cell) to the time that the tumor becomes clinically detectable (one billion cells at least). Estimates of the time required for a single cell to divide a sufficient number of times to yield one billion cells are on the order of years. During this period, it is impossible to detect the cancer with any known test.



Original citation not available. K. Micetich, M.D.

Figure 1. Hypothetical growth curve of a cancer. The latent phase accounts for the majority of time that the tumor is present. The cancer cannot be detected during the latent phase.

4. **TUMOR CELL HETEROGENEITY.** Although the cancer cells look similar under the microscope, the cells can be categorized with respect to a number of different characteristics. When this is done, despite the amazing similarity under the microscope,

the cancer cells from the same tumor are very different from one another. This is **tumor cell heterogeneity**.

The appropriate analogy is the different races and cultures present in the human species. Despite the fact that we are all human, we are all different from one another with respect to personality, aggressiveness, hair color and other physical characteristics. Differences in personality and aggressiveness are not easy to measure and are not apparent at first glance. In fact, these characteristics require special testing and measuring tools. The same is true for cancer cells.

4a) Growth fraction: dividing cells/total cell number.

4b) Metastatic potential and metastatic process: Cancers cannot be detected until there are about 1 billion cancer cells located in the same area. The organ in which the cancer begins is termed the **primary site of the cancer.** Stomach or gastric cancer refers to a cancer that begins in the stomach. The diagnosis of breast cancer, lung cancer and kidney cancer, for example, means that the origin or the primary site of the cancer is breast, lung and kidney.

If cancers always remained localized to the organ in which the process began, most cancers would be cured. The problem is that cancer cells may and frequently do enter the blood stream and are transported by the blood stream to different organs. If the right factors are present, these migratory cancer cells from the primary cancer can grow in the new host organ. This process of spread is the **metastatic process**. Thus, cancer of the stomach may spread to the lungs. A patient in whom this has occurred has stomach cancer that has metastasized to the lungs. The patient does not have lung cancer. A patient with breast cancer whose disease has spread to the liver has metastatic breast cancer to the liver. This patient does not have breast cancer and liver cancer. The designation "liver cancer" means that the liver is the original site of the cancer.

The metastatic process takes time and frequently occurs during the subclinical or latent phase of the cancer. The steps in the metastatic process are (1) clonal evolution; (2) intravasation; (3) extravasation; (4) growth in the distant metastatic site.

The stage of a cancer indicates the extent of disease at the time of diagnosis and determines prognosis and treatment. The usual staging system is the TNM Classification. However, it is important to note that all staging systems reduce to three basic stages:

1. Cancer localized to the organ of origin
2. Cancer localized to the organ of origin with spread to the regional draining lymph nodes 3. Disseminated disease.

The stage assesses the risk that the cancer may have undergone the metastatic process during the subclinical or latent period of growth.

4c) Resistance to Chemotherapy:

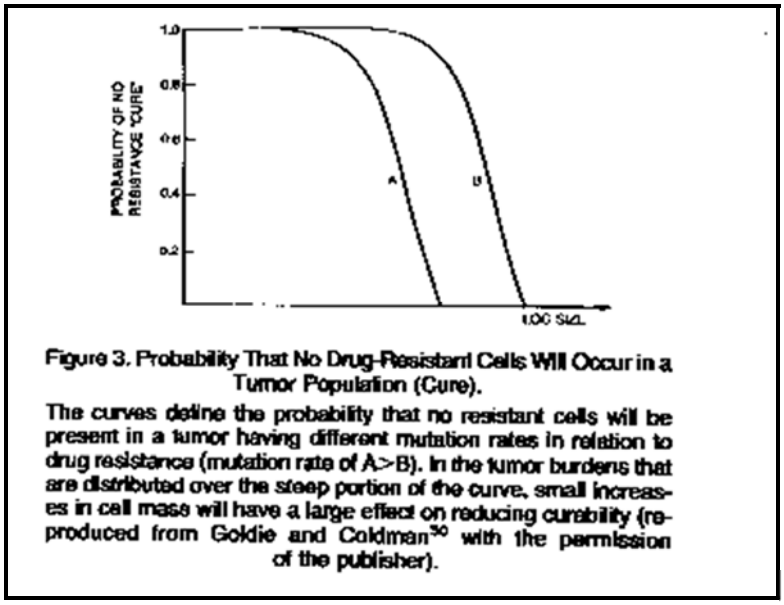


Figure 3. Probability That No Drug-Resistant Cells Will Occur in a Tumor Population (Cure).

The curves define the probability that no resistant cells will be present in a tumor having different mutation rates in relation to drug resistance (mutation rate of A>B). In the tumor burdens that are distributed over the steep portion of the curve, small increases in cell mass will have a large effect on reducing curability (reproduced from Goldie and Coldman[50] with the permission of the publisher).

Figure 2. Goldi-Coldman Hypothesis Original citation not available. K. Micetich, M.D.

Neoplastic cell resistance to chemotherapy occurs as a chance, spontaneous, event analogous to resistance of bacteria to antibiotics.

5. CHEMOTHERAPY: Chemotherapy drugs are developed, designed and selected to kill mammalian cells. Chemotherapy are drugs given to a patient with a malignant process. The goal is to reduce the total body cancer burden by killing cancer cells. If the process is completely eradicated (all cancer cells sensitive to chemotherapy), the patient will be cured. If the reduction in the total body cancer burden is incomplete (some of the cells were resistant to the chemotherapy) then the life of the patient may be prolonged.

It is not possible to target the antineoplastic drug only to the cancer cell. Thus, the drug is taken up by both the cancer cell and the normal cells. The effect of the drug on the normal cells is responsible for the **TOXICITY** or the side effects of the drug. The mechanism of action of the drug responsible for the lethal effect on the neoplastic cell (**CYTOTOXICITY**) may or may not be responsible for side effects of the drug since most drugs may affect more than one macromolecular target.

5a) Resistance to chemotherapy: Malignant cell resistance to chemotherapy accounts for the failure of chemotherapy to completely eradicate a malignant process.

The ability of chemotherapy to cure cancer is inversely proportional to the tumor burden (Skipper Hypothesis).

Chemocurable cancers never develop resistance to chemotherapy. Examples are disseminated testicular cancer, some lymphomas, some leukemia's and Hodgkin's disease.

Chemoresistance can develop at any time during the natural history of a cancer.

5b) Cell cycle specific and cell cycle non-specific drugs: Some chemotherapy drugs have an effect in only one part of the cell cycle. These agents are called cell cycle specific (CCS). Some chemotherapy drugs can act against a cancer cell at any point in the cell cycle. These agents are called cell cycle non-specific (CCNS).

5c) Assessment of response to chemotherapy:

Complete remission

Partial remission

Stable disease

Progression of disease

5d) Drug development:

Preclinical testing

Phase I clinical trials

Phase II clinical trials

Phase III clinical trials

5e) Scheduling: Effective cancer treatments require the repeated cyclical administration of drug or drugs (this will be discussed during a later lecture). The schedule of chemotherapy refers to the dose of drug (generally determined as the mg/M2 of body surface area, provides consistent toxicity across weights and heights), the route of administration (oral, subcutaneous, intravenous, intrathecal, intraperitoneal, intraarterial, etc.), and the length of a treatment cycle. Most chemotherapy drugs are given intravenously. Some treatments call for a daily infusion of drug for 5 days. Still others require three days of drug. Some drugs are given as a continuous intravenous infusion over 24 to 96 hours. Lastly, chemotherapy is usually repeated at 21 to 28 day intervals in order to allow the patient to recover from the side effects of the drug treatment. Sometimes the cytotoxicity of the drug (the efficacy of cancer cell kill) depends critically on the schedule of drug administration. This is termed **schedule dependent cytotoxicity.** In some cases the types of side effects the patient experiences is dependent upon the schedule. This is termed **schedule dependent toxicity**.

6. TOXICITY OF CHEMOTHERAPY:

6a) Constitutional toxicities:

Nausea and vomiting

Dexamethasone (side effects: elevated sugars, feeling of excess energy, flushing)

Prochlorperazine (extrapyramidal side effects)

Lorazepam

5-HT3 receptor antagonists (ondansetron, granisetron)

Side effects: QT prolongation occurs in a dose-dependent manner. Cases of Torsade de Pointes have been reported. Avoid ondansetron in patients with congenital long QT syndrome.
Constipation in about 9 % of patients. Headache and diarrhea can also occur.

Neurokinin 1 receptor antagonist in area postrema (aprepitant):
very effective in acute and delayed nausea and vomiting for highly emetogenic chemotherapy regimens.

Loss of appetite

Fatigue

6b) Toxicities due to effect of chemotherapy on normal dividing cells:

(a) transient myelosuppression [temporary depression of the blood cell counts resulting from killing of bone marrow precursor cells];

(b) temporary hair loss;

(c) transient gastrointestinal toxicity [mucositis or sore mouth, or diarrhea] due to an effect of the drug on the normal dividing cells of the oral and small intestinal mucosa;

Stomatitis supportive care:

Palliative care with mouth rinse:

- Diphenhydramine
- Maalox/Mylanta
- Viscous Lidocaine
- ± Glucocorticoids (Prednisone)

May also require treatment for oral fungal infection

- Nystatin oral suspension swish and swallow

Frequently requires narcotic pain medication

Self-limiting

Consider effect on oral intake (fluids and caloric)

Enteritis Supportive Care:

Maintain hydration

Antidiarrheal agents after infectious etiology excluded including c. diff diarrhea (assay for c.diff toxin)

- Loperamide (imodium)
- Diphenoxylate and atropine (lomotil) after infectious etiology excluded

Octreotide (IV or subcu) in severe cases

(d) sterility (which may be permanent) due to the effect of the drug on the dividing germ cell epithelium;

(e) second neoplasms due to the mutagenic effect of the drug on normal cells.

The above listed potential toxicities tend to be common to all drugs (see 6a and 6b). Exceptions will be noted. There is a great deal of individual patient variability with respect to the type of toxicity and the severity of the toxicity that he/she develops.

With the exception of nausea and vomiting which develop within hours of giving the anticancer drug, the toxicities are not acute in onset. The hair loss begins to occur two to three weeks after the first administration of drug. Myelosuppression is not noted until about 10 to 14 days following drug administration. Sore mouth and diarrhea, if they are to occur, are not usually noted until about 1 week following the treatment with chemotherapy.

6c) Organ specific toxicities.

cardiac toxicity of the anthracyclines

pulmonary toxicity of bleomycin

nephrotoxicity of cis-DDP).

6d) Myelosuppression: Myelosuppression is an important and potentially life threatening toxicity. Also for most drugs (exceptions will be noted) myelosuppression is the dose limiting toxicity. Dose limiting toxicity is that side effect which limits the amount of drug that can be given. Therefore, it is important to understand the side effect of myelosuppression.

The blood is composed of red blood cells which carry oxygen, the platelets which prevent bleeding and the white cells which combat infection. The class of white blood cells most responsible for fighting bacterial infections is the polymorphonuclear leukocyte or the segmented neutrophil (PMN, seg). "Bands" which are immature forms of the PMN are also important. At the time of administration of the chemotherapy, the bone marrow stops production of the three cellular elements to varying degrees in individuals. The red blood cell count is usually affected only minimally and severe anemia requiring transfusions as a result of administration of an anticancer drug is unusual. The platelets and the total white blood cell count and the PMN and band count generally fall 10 to 14 days following the administration of drug.

The fall in platelets and the white blood cell count (WBC) is not acute. This is because the effect of the chemotherapy is not on the formed elements of the blood but on the precursor cells in the bone marrow which are dividing. Thus, when chemotherapy is given, the production of the precursor cells of the platelets and the white blood cells is temporarily halted. However, the platelets and the PMN in the blood are not affected. So, after an anticancer drug is given, for about 1 week there is a decrease in the production of PMN and platelets and as the mature elements of the blood are removed from the circulation, there are no cells in the bone marrow ready to replace them. The bone marrow is back to normal about the third week following the administration of the chemotherapy. Thus, the blood counts usually recover between days 21 and 28 following the administration of chemotherapy.

Erythropoietin stimulating agents (ESAs) are commercially available (Epoetin alfa, darbepoetin alfa). The use of these agents does decrease the frequency of blood transfusions. These agents are approved for use in myelodysplastic syndromes and end stage renal disease. However, there is concern that the use of these agents to maintain hemoglobin levels in patients with cancer may be deleterious to survival and their use should be avoided.

The cyclical fall and rise in the total white blood cell count and the PMN and band count is shown in figure 3. Refer to example below. Drug is administered on day 1. The chart shows the total white blood cell count and the ANC **(the absolute neutrophil count determined by the following formula:**

ANC= total white count X (fraction of PMN + fraction of bands).

The ANC is an important number. If the ANC falls to less than 500 the patient is at increased risk of infection from endogenous bacteria. When the WBC count falls, these bacteria are no longer held in check and bacteremia may occur. Any patient who develops a fever >38.5oC and who has an ANC <500 must be hospitalized and started on broad spectrum antibiotics immediately until the ANC recovers to >500.

Myeloid Growth Factors: Filgrastim (daily subcutaneous injections) or peg-filgrastim (every three to four week administration) can be administered 24 hours after chemotherapy administration. These agents shorten the duration of neutropenia. They do not prevent neutropenia.

The platelets may also fall 10-14 days following the administration of an anticancer drug (See figure 4). The PMN count is usually affected more than the platelet count. If the platelet count falls to <10,000 platelet transfusions are usually given to maintain a platelet count of > 10,000. The platelet count recovers between days 21 and 28.

Megakaryocyte Growth Factors: Interluekin-11 (oprelvekin). Can decrease the frequency of platelet transfusions after chemotherapy. Major side effects include fluid retention and atrial arrhythmias. Not used often in the supportive care of the cancer patient due to expense and toxicity.

EXAMPLE: The patient was a 65 year old white female receiving doxorubicin (60 mg/M2) and vincristine (1.4 mg/M2) intravenously every three weeks.

She is 68 inches tall and weighs 160 pounds. From a nomogram, her BSA (body surface area) is determined to be 1.86 M2.

Therefore her dose of doxorubicin is 111.6 mg and that of vincristine is 2.6 mg. The chemotherapy was administered and weekly blood counts were obtained.

	Day 1	Day 8	Day 15	Day 22	Day 29
WBC	**7800**	**7500**	**2500**	**4000**	**6800**
Segs	**0.6**	**0.65**	**0.25**	**0.4**	**0.7**
Bands	**0.05**	**0.05**	**0**	**0.1**	**0.03**
ANC	**5070**	**5250**	**625**	**2000**	**4964**
Lymphs	**0.3**	**0.2**	**0.6**	**0.3**	**0.2**
Monos	**0.02**	**0.02**	**0**	**0**	**0.01**
Baso	**0.03**	**0.04**	**0**	**0**	**0.01**
Eos	**0**	**0.04**	**0**	**0**	**0.01**
Hemoglobin	**13.5**	**13.2**	**11.5**	**10.8**	**11.3**
Hematocrit	**0.42**	**0.41**	**0.35**	**0.31**	**0.35**
Platelets	**207000**	**198000**	**100000**	**125000**	**210000**

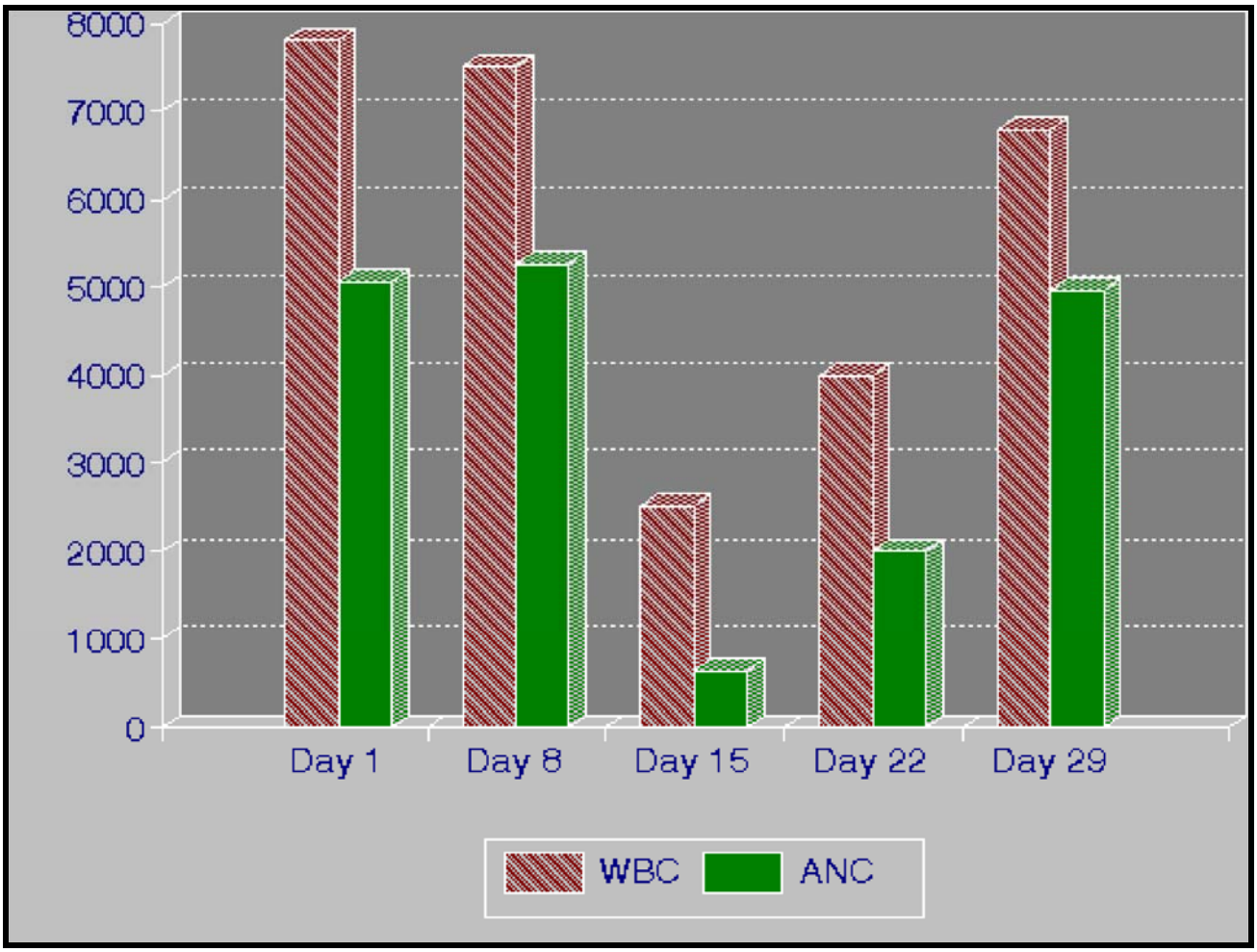


Figure 3. White cell and absolute neutrophil count as a function of time after chemotherapy

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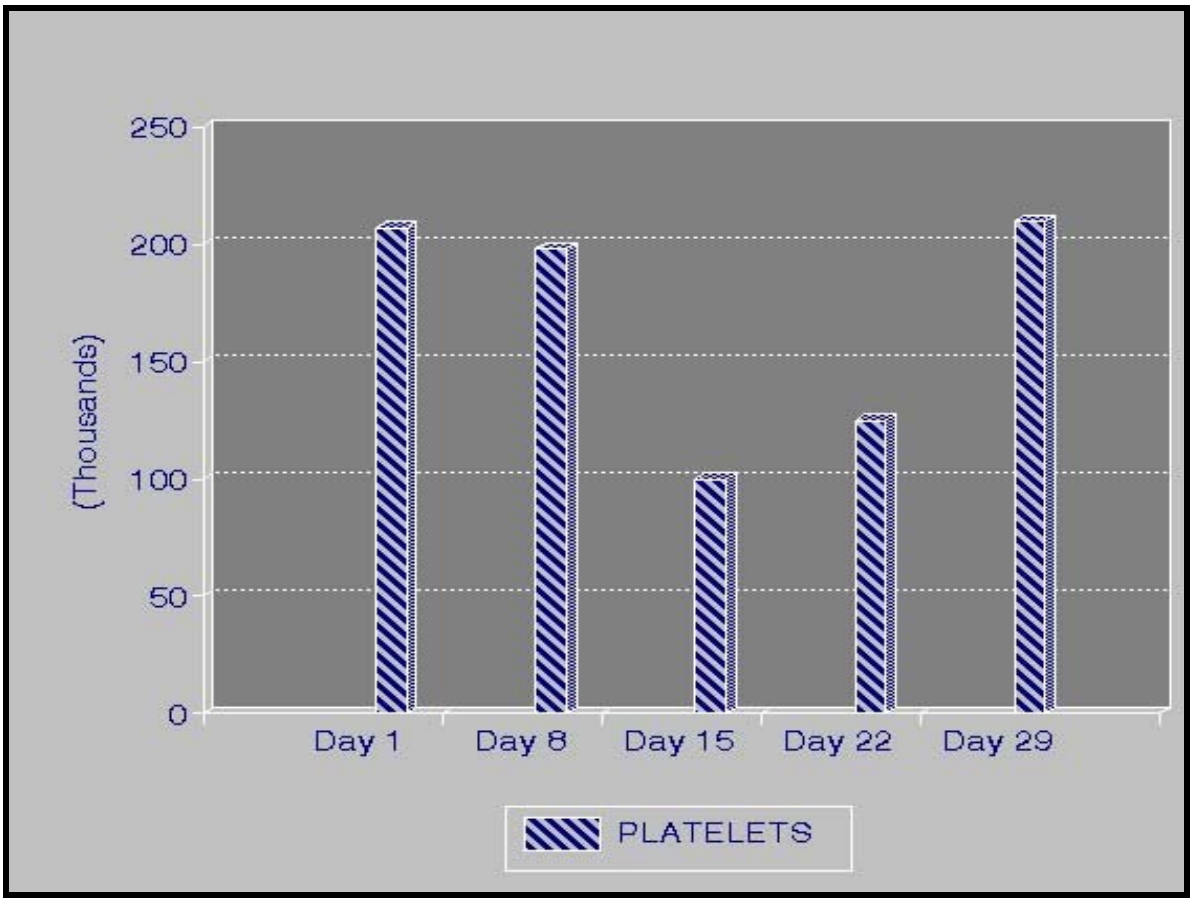

Figure 4. Platelet count as a function of time after chemotherapy

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6e) Cumulative toxicity: There is another type of toxicity associated with chemotherapy. This is called cumulative toxicity. This type of toxicity is seen with some drugs which damage a particular organ a small amount with each administration of drug. The damage is irreversible. With each drug administration the damage accumulates until at some point the organ cannot function properly because too much of it has been damaged. Examples of this type of toxicity are the cardiac toxicity related to anthracycline administration and the pulmonary toxicity associated with Bleomycin.

VESICANTS: Some chemotherapy drugs are vesicants.

- **Vesicant: A substance that causes tissue blistering. A blister agent. Also called a vesicatory. Vesicants are highly reactive chemicals that combine with proteins, DNA, and other cellular components to result in cellular changes immediately after exposure.**
- **Examples: vincristine, vinblastine, doxorubicin and danunorubicin**

7. REVIEW QUESTIONS:

1. A patient had a left hemicolectomy 3 years ago for a cancer of the sigmoid colon. At the time of surgery she was found to have had cancer spread to the regional draining lymph node and the cancer was removed. At the time of the surgery the liver was found to be free of cancer. She now presents to the clinic with weight loss, anorexia and jaundice. Physical examination reveals a jaundiced female with a liver span of 20 cm. The liver was nodular and non-tender. A CT scan of the liver shows multiple space occupying lesions in the liver. A needle biopsy of one of the lesions reveals poorly differentiated adenocarcinoma. Comparison of the pathology of the liver biopsy with that of the original colon primary cancer shows that the cells are morphologically similar.

   a) Does this patient have liver cancer or colon cancer that has metastasized to the liver? Explain.

   b) The patient is angry with your answer in (a). She states emphatically that the surgeon said that he had removed all of the tumor. At the time of surgery 3 years ago, did this patient have cancer in the liver? If so, how could it not have been detected? How is it that a cancer can return at a later date even if all the cancer is removed?

2. A patient has metastatic breast cancer to the liver and the bones and the left anterior chest wall. The left anterior chest wall lesion measures 5 X 4 cm. Chemotherapy is given and the lesion shrinks to 3 X 2 cm and then undergoes no further decrease in size despite the continued administration of chemotherapy. Explain why the cancer initially decreased in size and then underwent no further resolution despite continued chemotherapy administration.

3. A patient is going to undergo chemotherapy. Describe the general side effects that he or she may expect.

4. Patient A has metastatic testicular cancer. He has 2 pulmonary metastases each less than 2 cm in size and no palpable abdominal masses. Patient B has 2 pulmonary metastases each greater than 4 cm in size and a 6 cm palpable abdominal metastatic mass. Both are treated with the same chemotherapy. Which patient has the higher cure rate with chemotherapy? Why? (hint: consider which patient is likely to have the higher tumor burden and relate this to the Goldie Coldman hypothesis and the Skipper hypothesis).

5. Consider that two patients each have a cancer that began on January 1, 1995 and were discovered as 3 cm pulmonary masses on January 1, 1998. Both undergo surgical removal of the cancers.

Patient A has a squamous cell lung cancer that is well-differentiated, shows no necrosis and rare mitoses.

Patient B has a squamous cell lung cancer that is poorly differentiated, shows necrosis and many mitoses.

a) Which patient is more likely to be cured with surgery? Why?

b) Which patient is more likely to have developed chemoresistant clones of cells? Why?

(hint: consider the significance of necrosis and the comparative number of cell divisions needed in patient A and B to produce a 3 cm cancer and relate this to the concept of tumor cell heterogeneity).

6. Discuss what is meant by the stage of a cancer. What is its significance?

7. A patient receives chemotherapy on day 1. On day 15 he calls you and reports a fever of 39.5 o C. and shaking chills. What do you think is happening and what do you advise?

CHEMOTHERAPY II: ALKYLATING AGENTS

Date: April 10, 2014 – 8:30 am

Reading Assignment: Katzung-pp. 953-958; 962-964.

KEY CONCEPTS & LEARNING OBJECTIVES

1. Describe the mechanism of action of the alkylating agents 2.
Recognize the drugs that are classified as alkylating agents.
3. List the toxicities of cyclophosphamide.
4. Define the utility of mesna when administered with an alkylating agent.
5. Compare and contrast the toxicities of carboplatin, cisplatin and oxaliplatin.
6. Describe the mechanism of action of vincristine, paclitaxel and etoposide.
7. List the toxicities of vincristine, paclitaxel and etoposide.
8. List those drugs covered in this lecture that require dose modification due to renal insufficiency or jaundice.

DRUGS COVERED IN THE LECTURE

1. Cyclophosphamide
2. Ifosfamide
3. Cis-diaminedichloroplatinum (II)
4. Carboplatin
5. Oxaliplatin
6. Vincristine
7. Vinblastine
8. Vinorelbine
9. Paclitaxel
10. Albumin bound paclitaxel
11. Docetaxel
12. Cabazitaxel
13. Etoposide

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CHEMOTHERAPY II: ALKYLATING AGENTS AND PLANT ALKALOIDS

1. ALKYLATING AGENT OVERVIEW: Alkylating agents bind covalently to the DNA and therefore are all cell cycle non-specific. The drugs produce DNA-drug interstrand and DNAdrug intrastrand crosslinks.

The class of drugs termed **bis(chloroethyl)amines** includes cyclophosphamide, mechlorethamine (nitrogen mustard), chlorambucil and melphalan. These drugs are all bifunctional alkylating agents and preferentially alkylate the N-7 position of guanine.

The class of drugs termed the **nitrosoureas** includes BCNU and CCNU. BCNU and CCNU are bifunctional alkylating agents. These drugs alkylate the N-7 position of guanine. However, the critical alkylation site is the O-6 position of guanine. BCNU and CCNU will be cross-resistant but the nitrosoureas are generally only partially cross-resistant with the bis(chloroethyl)amines. Resistance to the nitrosoureas is due to constitutively high levels of a repair suicide enzyme termed an alkyltransferase. These drugs were of interest because they are lipophilic and cross the blood brain barrier and were developed to treat glioblastoma and other brain tumors. Their clinical use has declined due to the availability of temozolomide for the treatment of brain tumors. The nitrosureas will not be discussed.

The class of drugs termed the platinum coordination compounds are also bifunctional alkylating agents. Alkylation occurs primarily at the N-7 position of guanine.

The alkylating agents are cell cycle non-specific (CCNS) and are felt to produce cytotoxic effects by interstrand and intrastrand crosslinking of DNA.

Resistance to the alkylating agents can be due to nucleotide excision repair enzymes and binding of the alkylating agent to sulfur containing compounds.

2. ALKYLATING AGENTS:

a) Cyclophosphamide

a) Name, class: Cyclophosphamide, bifunctional alkylating agent (oxazaphosphorine) **b) Cycle specificity:** CCNS

c) Macromolecular target: DNA

d) Bioactivation if necessary: Cyclophosphamide must be activated by microsomal enzymes (P-450 oxidase) to 4-hydroxycyclophosphamide which is in equilibrium with aldophosphamide. Aldophosphamide is non-enzymatically cleaved to acrolein and phosphoramide mustard.

e) Mechanism of action: Phosphoramide mustard bifunctionally alkylates the N7 position of guanine and can form interstrand and intrastrand crosslinks.

f) Pharmacokinetics and metabolism: Metabolites are excreted into the urine.

g) Side Effects (toxicity): Nausea, vomiting, hair loss, myelosuppression, hematuria.

h) Special features and dose modifications:

(a) Hematuria is occasionally a problem. The major metabolite responsible for blood in the urine is acrolein. Preventive strategies include (1) administering the drug in the morning, drinking 6-8 glasses of water a day and urinating frequently; (2) continuous bladder irrigation (when used in high dose); (3) the use of mesna (uroprotective agent, see iphosphamide below).

(b)Most alkylating agents have been associated with the occasional occurrence of acute leukemia due to the mutagenic effects of the drugs.

(c) No guidelines for dose modifications due to renal or hepatic dysfunction.

i) Uses: Breast cancer, non-Hodgkin's lymphoma. Cyclophosphamide can be given intravenously as well as orally.

j) Other compounds in this class: Other alkylating agents in this class include nitrogen mustard, chlorambucil and melphalan. They all have myelosuppression as dose limiting toxicity.

Chlorambucil and melphalan are given orally and are used in the chronic treatment of some types of cancers (chronic lymphocytic leukemia, multiple myeloma).

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b) Ifosfamide

a) Name, class: ifosfamide, alkylating agent; isomer of cyclophosphamide
b) Cycle specificity: CCNS
c) Macromolecular target: DNA
d) Bioactivation if necessary: Same as cyclophosphamide.
e) Mechanism of action (cytotoxicity): DNA crosslinking.
f) Pharmacokinetics and metabolism: Excreted via the urine.
g) Side effects (toxicity): Myelosuppression is dose limiting. At high doses the patients may develop lethargy and confusion. Nausea, vomiting and hair loss. **h) Special features and dose modifications:**

(a) Because this drug produces hemorrhagic cystitis regularly, the drug is always coadministered with MESNA (HS-CH2-CH2-SO3-Na+). In the blood, the molecule dimerizes and is inactive. In the urine, the dimer is hydrolyzed and the monomer binds to acrolein and other alkylating agent metabolites. The same strategy can also be employed for the prevention of hemorrhagic cystitis associated with high dose cyclophosphamide.

(b) No guidelines for dose modifications due to renal or hepatic dysfunction.

i) Uses: The drug is used for the treatment of sarcomas and relapsed testicular cancer.

j) Other compounds in this class. See cyclophosphamide.

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c) Temozolomide

a) Name, class: Temozlomide, alklating agent (monofunctional)
b) Cycle Specificity: CCNS
c) Macromolecular Target: DNA
d) Bioactivation if necessary: spontaneous hydrolysis to the DNA reactive species.
e) Mechanism of action (cytotoxicity): The DNA reactive species methylates the DNA and inhibits DNA function and DNA synthesis.
f) Pharmacokinetics and metabolism: One third of administered dose is recovered from the urine.
g) Side effects (toxicity): Myelosuppression is dose limiting. Nausea, vomiting, hair loss.
h) Special features and dose modifications:

(a) Dose modifications will be for myelosuppression

(b) The drug can be given orally or intravenously.

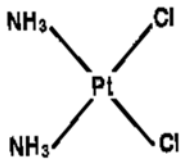
(c) The drug can be given with radiation therapy treatments. When given over a prolonged period of time prophylaxis for pneumocystis carinii pneumonia is required.

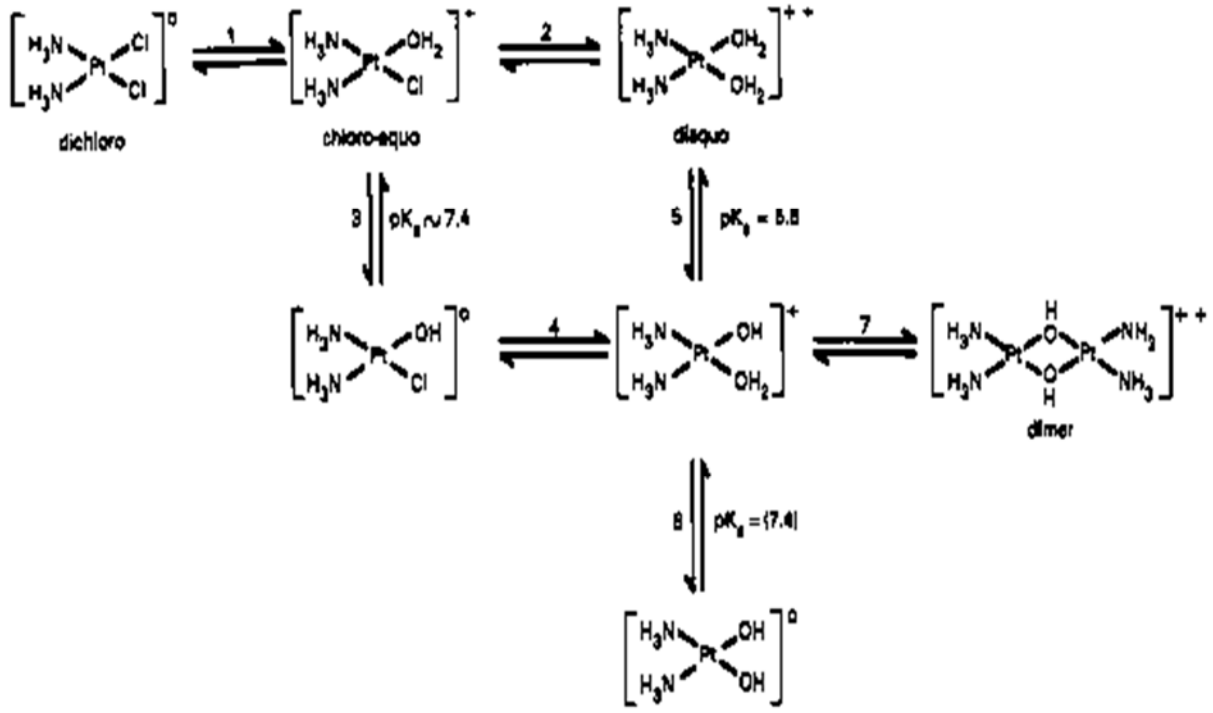
(d) No guidelines for dose modifications due to renal or hepatic dysfunction.

i) Uses: Malignant brain tumors.
j) Other compounds in this class: none.

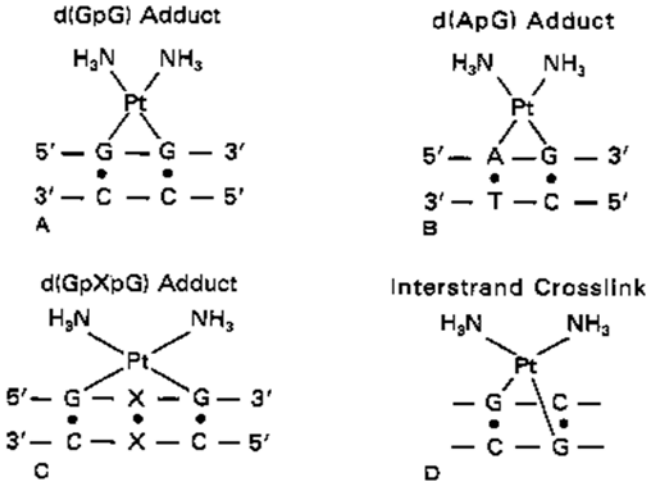
d)Cis-diaminedichloroplatinum (II)

a) Name, class: Cis-diaminedichloroplatinum (cisplatin), bifunctional alkylating agent **b) Cycle specificity:** CCNS
c) Macromolecular target: DNA
d) Bioactivation if necessary: The parent compound is not active. In solution in the presence of low chloride ion concentration, the molecule undergoes sequential aquation.





e) Mechanism of action (cytotoxicity): Binds covalently to DNA to produce cytotoxic interstrand and intrastrand crosslinks.



f) Pharmacokinetics and metabolism: Tightly bound to proteins in the plasma. Excretion is via the kidneys.

g) Side effects (toxicity): Intense nausea and vomiting. Renal toxicity is dose limiting.

The drug produces myelosuppression in < 25 % of patients. The drug frequently causes hypomagnesemia. Peripheral neuropathy is seen in < 5 % of patients. 8th cranial nerve damagehigh frequency hearing loss. Allergic reactions.

h) Special features:

(a) To avoid renal damage, the drug is given with saline/mannitol diuresis. It has been known for some time that chloruresis protects the kidneys. Because the drug must be given with hydration, patients with pre-existing cardiac/pulmonary problems may not be able to tolerate the drug and the hydration.

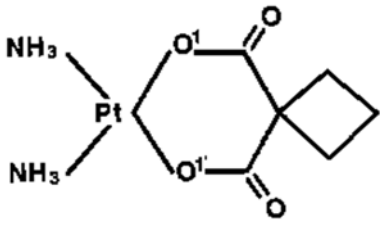
(b) Dose reductions of the drug are necessary for patients with renal insufficiency.

i) Uses: Testicular cancer, bladder cancer, head and neck cancer, ovarian cancer, small cell and non-small cell lung cancer.

j) Other compounds in this class:

Carboplatin, cis-diammine-1,1-cyclobutane-dicarboxylato-platinum (II). This compound produces the same DNA lesions as does the parent compound. The kinetics of crosslinking differs. Carboplatin produces the same lesions as cisplatin but takes longer to form the cross links. Therefore, cisplatin and carboplatin will be cross-resistant.

Unlike cisplatin, carboplatin is not renal toxic. Carboplatin is excreted via the kidney. Dose limiting toxicity of carboplatin is myelosuppression. There is a linear relationship between carboplatin plasma clearance and glomerular filtration rate.



Carboplatin

Unlike the other chemotherapy drugs, carboplatin dose is calculated using a targeted AUC (area under the curve, free carboplatin plasma concentration X time; mg/ml/min). There is a relationship between the AUC and toxicity (thrombocytopenia) and response. In practice we aim for AUC values from 5-7 mg/ml/min.

The dose of carboplatin is calculated as:

dose (mg)=AUC X (GFR +25).

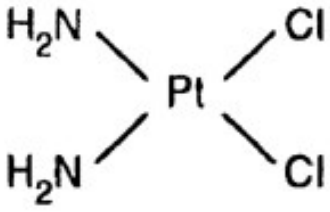
A web site that calculates the dose is:
http://hccapps.musc.edu/hemonc/carboplatin_dose_calculator.htm

The drug does not have to be given with saline hydration and is a good alternative to cisplatin when organ dysfunction precludes the use of cisplatin.

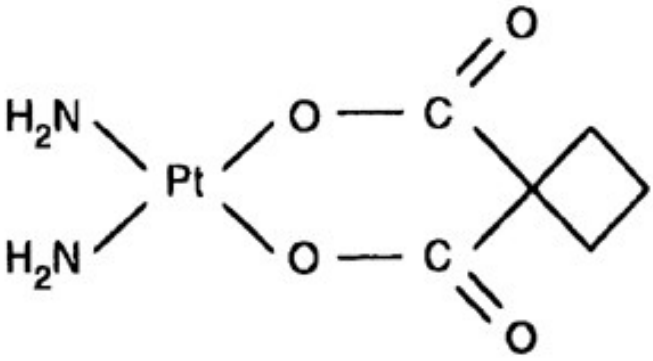
Testicular cancer, bladder cancer, head and neck cancer, ovarian cancer, small cell and nonsmall cell lung cancer.

Oxaliplatin. Oxalato(1,2-diaminocyclohexane)platinum (II)

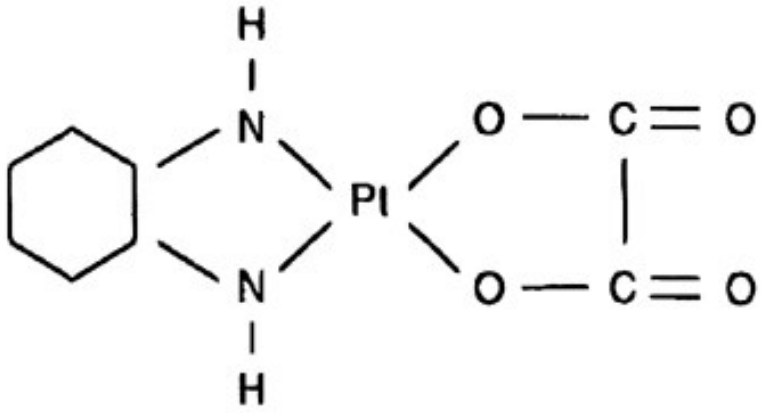
Carrier Ligand Core Leaving Group



Cisplatin



Carboplatin



Oxaliplatin

Oxaliplatin is a third generation platinum coordination compound. It is excreted via the kidneys and is not nephrotoxic. Myelsuppression is common but not severe. Dose limiting toxicity is neurotoxocity: acute and chronic sensory. The acute neuropathy begins during the drug administration, is cold induced (paresthesias, electric shock like sensations in the extremities when cold, laryngeal dysesthesia when drinking cold liquids) and lasts about a week or so after drug administration. The chronic sensory neuropathy is a cumulative toxicity and occurs after repeated administrations of drug and consists of stocking and glove paresthesias. It does tend to get better with time but slowly and does not completely resolve.

Oxaliplatin is different from cisplatin and carboplatin in that it has significant antineoplastic activity against colorectal cancer.

PLANT ALKALOID OVERVIEW: Vincristine, vinblastine (periwinkle plant) and taxol (yew tree) are naturally occurring products termed plant alkaloids. Etoposide is semisynthetic.

Vincristine, vinblastine and taxol are cell cycle specific (M-phase) and either inhibit mitotic spindle formation (vincristine, vinblastine) or prevent breakdown of the mitotic spindle (taxol). There may be schedule dependent cytotoxicity associated with taxol and vincristine. Since these drugs act on a relatively brief phase of the cell cycle and are cell cycle specific, the drugs may best be given as a continuous infusion. Etoposide or VP-16 inhibits topoisomerase II and DNA strand breakage occurs.

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4. PLANT ALKALOIDS

a) Vincristine

a) Name, class: Vincristine, Plant alkaloid, spindle poisons.
b) Cycle specificity: CSS (M phase)
c) Macromolecular target: Tubulin
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): Binds to dimeric form of tubulin and prevents polymerization of tubulin and thus, microtubule assembly, and causes the dissolution of the mitotic spindle.
f) Pharmacokinetics and metabolism: Excretion is via the bile and patients with an elevated bilirubin require a dose reduction.
g) Side effects (toxicity): Neuropathy is dose limiting. Sensory and autonomic neuropathies (motor neuropathies are not common). Stimulation of antidiuretic hormone release may produce hyponatremia. Vincristine does not cause myelosuppression. Hair loss, nausea and vomiting are not a problem.
h) Special features and dose modifications: Dose reduction is necessary for elevated bilirubin.
i) Uses: Lymphoma, Hodgkin's disease, lymphoblastic leukemia.

Other compounds in this class: Vinblastine. The drug is much less neurotoxic than vincristine and has a dose limiting toxicity of myelosuppression (unlike vincristine). **Vinorelbine.** Vinorelbine is useful in lung cancer and breast cancer.

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b) Paclitaxel

a) Name, class: Paclitaxel, plant alkaloid.
b) Cycle specificity: CSS (M-phase)

c) Macromolecular target: tubulin
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): Prevents tubulin disassembly.
f) Pharmacokinetics and metabolism: Tightly bound to plasma proteins and excreted via the biliary system. Hepatic metabolism.
g) Side effects (toxicity): Myelosuppression is dose limiting. Nausea and vomiting, stomatitis, peripheral sensory neuropathy, myalgias and arthralgias. Hair loss. **h) Special features and dose modifications:**

(a) Patients receiving taxol must be premedicated with steroids, diphenhydramine and an H2 blocker to decrease the incidence of allergic reactions (due to polyoxyethylated castor oil vehicle needed to make paclitaxel soluble)

(b) Dose reductions necessary in the presence of hepatic dysfunction.
i) Uses: Ovarian cancer, non-small cell lung cancer, gastroesophageal cancer, breast cancer.
j) Other compounds in this class: docetaxol (useful in prostate cancer when combined with prednisone), albumin bound paclitaxel (no hypersensitivity reactions and less myelosuppression and less peripheral neuropathy), cabazitaxel (prostate cancer).

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c) Etoposide

a) Name, class: Etoposide (VP-16), plant alkaloid, podophyllotoxin
b) Cycle specificity: CSS (G1-S phase).
c) Macromolecular target: Topoisomerase II
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): **C**omplex of drug, DNA and topoisomerase II produces DNA strand breakage.
f) Pharmacokinetics and metabolism: Excreted via the kidneys and to a lesser amount the bile.
g) Side effects (toxicity): Nausea and vomiting, hair loss. Dose limiting toxicity is myelosuppression.
i) Special features and dose modifications:

(a) This drug is leukemogenic. Total doses of > 2 gm/M2 are associated with an increased incidence of treatment related leukemia.

(d) Dose reductions necessary for patients with abnormal kidney and hepatic function.

j) Uses: Testicular cancer, small cell lung cancer, lymphomas.
k) Other compounds in this class: None in use at the present time.

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5. REVIEW QUESTIONS:

1. Is there an advantage to using both a cell cycle specific drug and a cell cycle non-specific drug in the treatment of a patient with cancer? Explain.

2. Describe the characteristic toxicity of the oxazophorines. Describe two strategies for preventing this characteristic toxicity.

3. The alkylating agents do not have schedule dependent cytotoxicity. Why?

4. Contrast the mechanisms of action of vincristine and paclitaxel.

5. Which plant alkaloid is NOT a "spindle poison"?

6. What are the characteristics of cancer chemotherapeutic agents which might indicate that the drugs would have schedule dependent cytotoxicity?

7. For the drugs covered in this lecture, indicate which drugs require a dose reduction in the presence of jaundice.

8. For the drugs covered in this lecture, indicate which drugs require a dose reduction in the presence of renal insufficiency.

9. Discuss the mechanism of cytotoxicity for the bifunctional alkylating agents.

CHEMOTHERAPY III: ANTIBIOTIC/ANTI-TUMOR AGENTS

Date: April 10, 2014 – 9:30 am

Reading Assignment: Katsung: pp. 965-966 (camptothecins, antitumor antibiotics, anthracyclines, bleomycin); pp. 971-972 (breast cancer, prostate cancer).

Smith IE, Dowsett M. Aromatase Inhibitors in Breast Cancer. N Eng J Med 2003; 348:2431-42.

KEY CONCEPTS & LEARNING OBJECTIVES

1. Describe the mechanism of action of doxorubicin and daunomycin
2. Describe the cumulative cardiac toxicity of doxorubicin and indicate the schedule dependency of this toxicity.
3. State the mechanism of excretion of doxorubicin and indicate the importance of this route of excretion in the safe treatment of cancer patients.
4. List some of the cancers in which doxorubicin or daunorubicin treatments are useful.
5. List the two types of diarrhea that may occur after treatment with irinotecan and their treatment.
6. Describe the pulmonary toxicity of bleomycin; indicate why high inspired oxygen concentrations be avoided in patients treated with bleomycin
7. Describe the mechanism of action and list the side effects of a selective estrogen receptor modulator and an aromatase inhibitor.
8. Define the prediive testing done on cancer tissue that may indicate responsiveness to a hormonal therapy.
9. State the indications for treatment with tamoxifen, anastrozole and leuprolide acetate.
10. Describe the “flare reaction” that can be seen with leuprolide acetate and how it can be mitigated.

DRUGS COVERED IN THE LECTURE

1. Doxorubicin
2. Bleomycin
3. Prednisone, dexamethasone
4. Flutamide, bicalutamide
5. Leuprolide acetate, goserelin
6. Anastrozole
7. Tamoxifen

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CHEMOTHERAPY III ANTIBIOTIC/ANTI-TUMOR AGENTS

1. ANTIBIOTIC ANTITUMOR AGENTS.

a) Doxorubicin

a) Name, class: Doxorubicin, antitumor antibiotic
b) Cycle specificity: CCNS
c) Macromolecular target: DNA
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): Intercalation between base pairs of DNA leading to strand breaks due to inhibition of topoisomerase II.

Topoisomerase II inhibiting drugs can be intercalators (daunomycin, doxorubicin, mitoxantrone, dactinomycin) or non-intercalators (etoposide).

There are topoisomerase I inhibiting drugs that have recently been approved for use (topotecan and irinotecan).

Topoisomerase I: Single strand DNA breaks, relaxation of the strand and re-anneal the strands.

Topoisomerase II: Double strand breaks in the DNA, relaxation and re-anneal the strands of DNA.

f) Pharmacokinetics and metabolism: Metabolized by the liver and excreted as a thiol adduct into the bile.

The intercalating and non-intercalating topoisomerase II inhibitors and the tubulin inhibitors (vinca alkaloids) are all cross resistant due to MDR (multidrug resistance). The P-glycoprotein is a membrane bound efflux pump. Giving some of these drugs as continuous infusions may downregulate the glycoprotein and reverse resistance. Quinine, verapamil, cyclosporine may block the efflux pump and reverse resistance.

g) Side-effects (toxicity): Nausea and vomiting and hair loss, stomatitis. Myelosuppression is dose limiting toxicity. Cardiac toxicity : congestive cardiomyopathy. Determine ejection fraction (ECHO or MUGA scan) prior to institution of treatment with doxorubicin. **h) Special features and dose reductions:**

(1) The drug is a vesicant.

(2) Must dose reduce in the presence of jaundice.

(3) The drug has a cumulative cardiac toxicity.

Cumulative toxicity refers to a toxicity which irreversibly damages a small part of an organ. With repeated administrations of drug the damage accumulates and after a certain dose is reached the total damage results in organ dysfunction.

A graph of the probability of a clinical event occurring (pulmonary toxicity, heart failure) as a function of the total dose (cumulative) of drug is termed a **cumulative toxicity curve.**

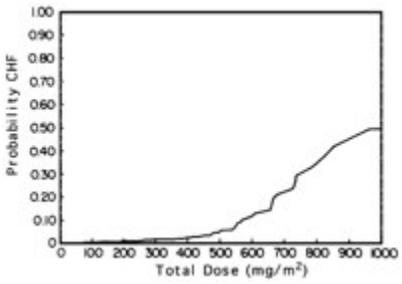

Figure 1. Probability of developing congestive heart failure as a function of the total dose of Adriamycin. Original citation not available. K. Micetich, M.D.

The curve seems to rise sharply once a dose of 550 mg/M^2 is reached. The data for this curve was obtained from patients receiving a dose of 60 mg/M^2 intravenously over 20 minutes every 3 weeks.

At a total dose of 550 mg/M^2 (9 administrations of drug) about 10 % of patients will have congestive heart failure. Because of the danger of developing congestive heart failure, we will usually not exceed a total **LIFETIME** dose of doxorubicin of 400 mg/M^2.

Subsequent research has shown that the probability of developing congestive heart failure is a function of the length of the infusion of the dose of the drug. A 96 hour infusion of drug is associated with much less cardiac toxicity than the same dose administered over 30 minutes.

Thus, doxorubicin manifests **schedule dependent cardiac toxicity.** Altering the schedule of administration does not alter the antitumor effect of the drug. Therefore, doxorubicin administration demonstrates **schedule independent cytotoxicity.**

The presumed mechanism of action of cardiac toxicity is free radical damage. Free radical damage is greater to the heart when you have very high plasma concentrations of drug (when the drug is given over 30 minutes). Free radical damage by the drug is minimized when you give the same dose of drug over 96 hours since high plasma levels of doxorubicin are not achieved. The free radical damage may be due to complexes of iron with doxorubicin.

This strategy of altering the schedule of administration of doxorubicin to prevent cardiac toxicity works only because the mechanism of cardiac toxicity (free radical damage) is different from the mechanism of cytotoxicity.

Most recently a drug called dexrazoxane (ICRF-187, Zinecard) has been approved by the Food and Drug Administration as a cardioprotective agent in patients receiving doxorubicin. The drug is an avid iron chelator and presumably the iron binds to the dexrazoxane rather than the doxorubicin and free radical damage is averted.

Prior mediastinal irradiation and long standing uncontrolled hypertension increases the risk of developing anthracycline cardiac toxicity.

i) Uses: Breast cancer, leukemia, sarcoma, Hodgkin's and non-Hodgkin's lymphomas.

j) Other compounds in this class: Daunomycin, idarubicin, epirubicin and Mitoxantrone. Daunomycin is less cardiac toxic than doxorubicin but is the less effective agent against solid tumors. Daunomycin is used in the treatment of some leukemias and is not used in the treatment of solid tumors. Idarubicin and epirubicin are used exclusively in leukemia and are analogs of doxorubicin that seems to be associated with less cardiac toxicity than is doxorubicin. All the anthracycline antibiotics are associated with dose limiting myelosuppression.

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b) Irinotecan

a) Name, class: Irinotecan, (camptothecin, plant alkaloid)

b) Cycle specificity: CCNS

c) Macromolecular target: DNA

d) Bioactivation if necessary: Prodrug. Converted by carboxylesterase to 7-ethyl-10hydroxycamptothecin (SN-38).

e) Mechanism of action (cytotoxicity): Topoisomerase I inhibition leading to single strand breaks in the DNA.

f) Pharmacokinetics and metabolism: Hepatic metabolism is significant. Dose reduction required for jaundice. UGTIAI is responsible for the clearance by glucuronidation of drug (irinotecan) and bilirubin.

The natural function of UGT1A1 is the catalysis of bilirubin glucuronidation. A genetic polymorphism in the UGT1A1 promoter (UGT1A1*28) results in enzyme underexpression, causing an impairment of bilirubin metabolism (reduced glucuronidation), clinically recognized as Gilbert.s syndrome (UGT1A1 7/7 genotype). Case reports describing severe neutropenia in Gilbert.s patients receiving standard starting doses of irinotecan suggested a link between this UGT1A1 polymorphism and irinotecan toxicity. (from **Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity: ACPS November 3, 2004 Advisory Committee Meeting).**

A mutation seen in 9 % of Caucasian and African populations decreases glucoronidation and genotyping is commercially available. Clinical guidelines do not exist for dose optimization as a function of genotype.

g) Side effects (toxicity): Nausea, vomiting and myelosuppression (dose limiting). Stomatitis and hair loss.

Early cholinergic diarrhea (during drug administration or in the first 24 hours treated with atropine).

Late secretory diarrhea may occur 7-10 days later that is treated aggressively with Imodium. Deaths have occurred.

h) Special Features and dose reductions: Decrease dose of drug in the presence of jaundice.

i) Uses: Useful in GI tract malignancies

j) Other compounds in this class: Topotecan used to treat ovarian cancer patients who have become resistant to carboplatin and paclitaxel.

c) Bleomycin

a) Name, class: Bleomycin, antitumor antibiotic.

b) Cycle specificity: CCS (G2-M phase).

c) Macromolecular target: DNA

d) Bioactivation if necessary: None.

e) Mechanism of action (cytotoxicity): Binds to DNA, free radical production leading to single and double strand DNA breaks. The bleomycin-iron form is the active species.

f) Pharmacokinetics and metabolism: About 50 % of the drug is excreted in the urine. The liver and the kidneys rapidly inactivate the drug (bleomycin hydrolase). The lungs and the skin have very low levels of the inactivating enzyme.

g) Side effects (toxicity): Pulmonary toxicity is dose limiting. Hyperpigmentation of the skin, hyperkeratosis of the palms. Stomatitis and hair loss. The drug is NOT myelosuppressive. The drug can cause a decrease in the pulmonary diffusion capacity. Anaphylactoid reactions have been noted with the first dose in patients with lymphoma. Fever and chills are common.

h) Special features and dose modifications: (1) test dose is given before the first dose is administered to monitor for severe reactions. (2) This drug has a cumulative pulmonary toxicity

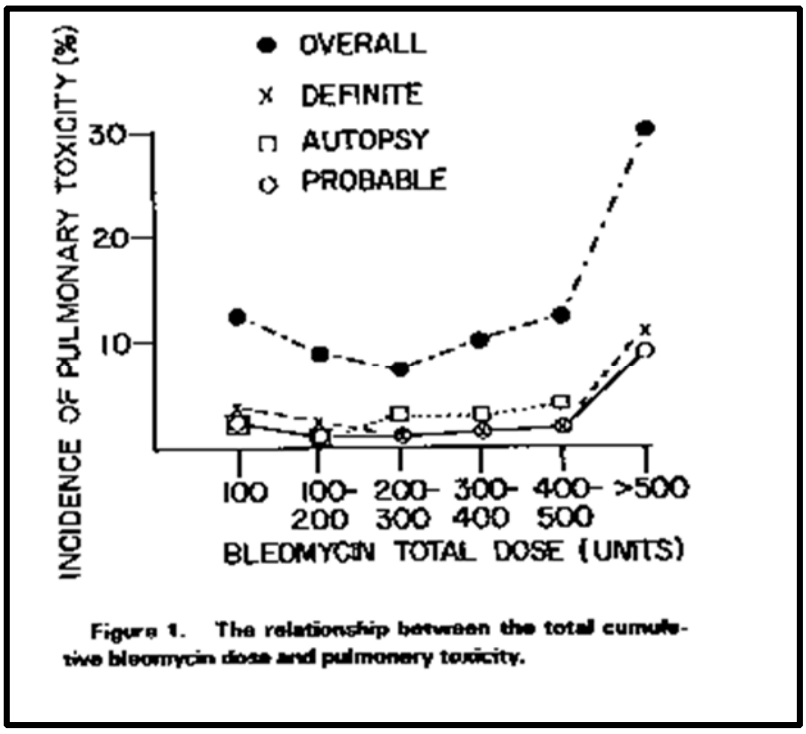

Figure 1. The relationship between the total cumulative bleomycin dose and pulmonary toxicity.

Figure 2-B. Incidence of pulmonary toxicity as a function of total bleomycin dose. Original citation not available. K. Micetich, M.D.

The incidence of bleomycin pulmonary toxicity rises sharply after a total dose of 400 units. The usual administration is 30 units per dose. This is about 13 administrations of drug. Clinically we do not exceed 400 units total dose. Obtain pulmonary function tests prior to institution of treatment. Also can monitor effect of bleomycin on the lungs with diffusion capacity of carbon monoxide.

(3) The drug may be given intravenously, intramuscularly, subcutaneously, or intracavitary (pleural space for palliation of a pleural effusion).

(4) When patients with history of bleomycin administration are given high inspired oxygen concentrations, there is a risk of pulmonary damage and death. If oxygen is necessary administer the lowest FiO2 to maintain oxygen saturation > 90 %.

(5) A dose reduction must be made for renal insufficiency.

j) Uses: The main use for this agent now is in the treatment of testicular cancer. A standard dose is 30 units (30 mg) intravenously weekly for 12 weeks. The drug has been used in the past in the treatment of lymphoma and squamous cell cancers (head, neck, vulva, cervix). However, its use now is principally confined to the treatment of testicular cancer. **k) Other compounds in this class:** None approved.

2. HORMONAL AGENTS

Overview: Prednisone is a steroidal agent that is useful in the treatment of antineoplastic diseases.

Breast cancer (in some patients) and prostate cancer (in most patients) are hormone dependent cancers. The tumors of about 60 % of women with breast cancer contain estrogen and progesterone receptors. These cancers require estrogen for continued growth. Depriving the cancer of estrogen can cause tumor regression. 60 % of women whose breast cancer contains the estrogen receptor protein will respond to a hormone therapy.

Prostate cancer is a hormone dependent neoplasm. Depriving the prostate cancer cells of androgen will produce a favorable response in 80 % of men.

a) Prednisone

a) Name, class: Prednisone, steroid.
b) Cycle specificity: N/A.
c) Macromolecular target: Steroid receptor.
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): Unknown.
f) Pharmacokinetics and metabolism: N/A.
g) Side effects (toxicity): Euphoria, weight gain, increased appetite, mania, hypertension, sodium and fluid retention, aggravation of diabetes, hypokalemia, alteration of the sleep-wake cycle, peptic ulceration of the stomach, spontaneous colon perforation, cataracts, osteoporosis, cushingoid appearance, and suppression of the pituitary-adrenal axis. **h) Special features and dose modifications:** None.
i) Uses: Prednisone, 100 mg/day or more, is useful in the treatment of Hodgkin's disease and non-Hodgkin's lymphoma. It is also used in the treatment of multiple myeloma and some leukemias.
j) Other compounds: Dexamethasone (less mineralicoroticoid effects than prednisone) is used to reduce cerebral edema in patients with brain metastases. Dexamethasone also potentiates the effect of 5-HT3 receptor antagonists (ondansetron) and is therefore used for control of emesis and nausea in patients receiving chemotherapy.

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b) Tamoxifen

a) Name, class: Tamoxifen, hormonal agent. (SERM: selective estrogen receptor modulator) **b) Cycle specificity:** N/A.
c) Macromolecular target: Estrogen receptor in cancer (usually breast cancer). Mixed agonist/antagonist with respect to the estrogen receptor.
d) Bioactivation if necessary: Tamoxifen is a prodrug and is metabolized in the liver to 4-hydroxytamoxifen, the active metabolite.
e) Mechanism of action (cytotoxicity): Binds to the estrogen receptor in the cancer cell.

f) Pharmacokinetics and metabolism: Metabolized by the liver.

g) Side effects (toxicity): Some weight gain, hot flashes, endometrial cancer, thrombosis. **h) Special features:**

(1) Tamoxifen is approved as a chemoprevention in women at high risk of developing breast cancer.

(2) The drug is also mildly estrogenic. It has a favorable effect on the lipid profile and decreases the rate of bone loss in postmenopausal women.

i) Uses: Tamoxifen is given orally 20 mg daily and is used exclusively in the treatment of breast cancer (metastatic or adjuvant setting). It can also prevent breast cancer.

j) Other compounds in this class: Raloxifene (chemoprevention of breast cancer).

c) Anastrozole

a) Name Class: Anastrozole, aromatase inhibitor

b) Cycle specificity: not applicable

c) Macromolecular target: Aromatase

d) Bioactivation if necessary: None

e) Mechanism of action: Selective non-steroidal inhibitor of aromatase produces marked lowering of plasma estrogen levels.

f) Pharmacokinetics and metabolism: Estradiol levels reduced 70% after 24 hours and 80% after two weeks of therapy. Metabolized extensively by the liver. No dose adjustments necessary in liver or renal dysfunction.

g) Side effects: Hot flashes, mood disturbance, arthritis, arthralgias, bone pain, bone loss, osteoporosis.

h) Special features: None

i) Uses: Oral administration. Hormone receptor positive breast cancer (adjuvant and metastasis).

j) Other compounds in this class: Letrozole, exemestane

e) Flutamide

a) Name, class: Flutamide

b) Cycle specificity: N/A.

c) Macromolecular target: Receptor.

d) Bioactivation if necessary: None.

e) Mechanism of action (cytotoxicity): Flutamide inhibits the uptake and binding of the testosterone to specific receptors in hormonally sensitive prostate cancer cells. **f) Pharmacokinetics and metabolism:** None relevant.

g) Side effects (toxicity): The drug is well-tolerated. Diarrhea (up to 20 % of patients) and elevations of the liver transaminases. **h) Special features:** None.

i) Uses: Oral administration and used in the ADT (androgen deprivation treatment) therapy of metastatic prostate cancer.

j) Other compounds in this class: Bicalutamide, nilutamide (similar to flutamide with less diarrhea)

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f) Leuprolide acetate

a) Name, class: Leuprolide, GnRH receptor agonist.
b) Cycle specificity: N/A.
c) Macromolecular target: Receptor.
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): Leuprolide binds to pituitary GnRH receptors and initially produces an increase in LH and FSH leading to an increase in testosterone and thus initially can stimulate tumor growth. By interrupting the normal pulsatile stimulation of the GnRH receptors, leuprolide down regulates the secretion of gonadotropins LH and FSH, leading to a reduction in testosterone levels.
f) Pharmacokinetics and metabolism: None relevant.
g) Side effects (toxicity): Hot flashes. General side effects of androgen deprivation therapy (ADT): weakenss, decreased libido, loss of muscle mass, erectile dysfunction, change in body fat distribution, gynecomastia
h) Special features: There may be an initial worsening of symptoms in patients with cancer of the prostate since testosterone production initially increases before decreasing. Therefore, the patient is treated with flutamide or bicalutamide for 2-4 weeks before institution of leuprolide acetate treatment (depot injections). The flutamide or bicalutamide are then discontinued. **i) Uses:** The drug is given intramuscularly. Depot injections are available.
j) Other compounds in this class: Goserelin (agonist of LHRH).

REVIEW QUESTIONS:

1. Define the mechanism responsible for MDR.

2. List the drugs that are cross resistant if MDR is the primary mechanism of resistance.

3. A patient with prostate cancer metastatic to the bone is started on leuprolide. Two weeks later he calls you and states that his bone pain is severe. Discuss the mechanism of worsening bone pain in this patient and indicate what could have been done to prevent the problem.

4. Define intercalation.

5. What is a vesicant?

6. Define and explain the concept of schedule dependent cardiac toxicity of doxorubicin.

7. What is the mechanism of cytotoxicity of doxorubicin?

8. A patient with breast cancer has jaundice due to metastatic disease in the liver. Doxorubicin is given intravenously and the patient expires three weeks later of septic shock. Was doxorubicin a good choice for this patient? Why or why not?

CHEMOTHERAPY III: ANTIBIOTIC/ANTI-TUMOR AGENTS

Date: April 10, 2014 – 9:30 am

Reading Assignment: Katsung: pp. 965-966 (camptothecins, antitumor antibiotics, anthracyclines, bleomycin); pp. 971-972 (breast cancer, prostate cancer).

Smith IE, Dowsett M. Aromatase Inhibitors in Breast Cancer. N Eng J Med 2003; 348:2431-42.

KEY CONCEPTS & LEARNING OBJECTIVES

1. Describe the mechanism of action of doxorubicin and daunomycin
2. Describe the cumulative cardiac toxicity of doxorubicin and indicate the schedule dependency of this toxicity.
3. State the mechanism of excretion of doxorubicin and indicate the importance of this route of excretion in the safe treatment of cancer patients.
4. List some of the cancers in which doxorubicin or daunorubicin treatments are useful.
5. List the two types of diarrhea that may occur after treatment with irinotecan and their treatment.
6. Describe the pulmonary toxicity of bleomycin; indicate why high inspired oxygen concentrations be avoided in patients treated with bleomycin
7. Describe the mechanism of action and list the side effects of a selective estrogen receptor modulator and an aromatase inhibitor.
8. Define the prediive testing done on cancer tissue that may indicate responsiveness to a hormonal therapy.
9. State the indications for treatment with tamoxifen, anastrozole and leuprolide acetate.
10. Describe the “flare reaction” that can be seen with leuprolide acetate and how it can be mitigated.

DRUGS COVERED IN THE LECTURE

1. Doxorubicin
2. Bleomycin
3. Prednisone, dexamethasone
4. Flutamide, bicalutamide
5. Leuprolide acetate, goserelin
6. Anastrozole
7. Tamoxifen

CHEMOTHERAPY IV: ANTI-METABOLITES

Date: April 14, 2014 – 8:30 am

Reading Assignment: Katzung: pp. 958-962

KEY CONCEPTS & LEARNING OBJECTIVES

1. State the mechanism of action of methotrexate, cytarabine and 5-fluorouracil
2. Describe the strategy of high dose methotrexate with leucovorin rescue and list the factors which are important to the safe implementation of this strategy.
3. List the antimetabolites that are approved for intrathecal administration.
4. Describe the rationale for the coadministration of 5-Flourouracil with leucovorin
5. Describe the metabolism of 5-flourouracil.
6. Describe the metabolism of 6-mercaptopurine
7. List some of the clinical indications for treatment with 5-flourouracil and leucovorin and 6-mercaptopurine
8. Describe the schedule dependent toxicity of cytarabine
9. List the toxicities of cytarabine and 5-flourouracil

DRUGS COVERED IN THE LECTURE

1. Methotrexate
2. Pemetrexed
3. Cytarabine
4. Gemcitabine
5. 5-Fluorouracil
6. Capecitabine
7. 6-mercaptopurine
8. 6-thioguanine

CHEMOTHERAPY IV: ANTI-METABOLITES

1. **OVERVIEW:** The antimetabolites are structural analogs of naturally occurring metabolites. Therefore, they can substitute for the naturally occurring metabolites in biochemical pathways and cause cessation of synthesis-usually of nucleic acids. The antimetabolites are cell cycle specific (acting during the S-phase).

2. ANTIMETABOLITES

a) Methotrexate

a) Name, class: Methotrexate, antimetabolite, antifolate.
b) Cycle specificity: CCS (S phase).
c) Macromolecular target: Dihydrofolate reductase.
d) Bioactivation if necessary: None.
e) Mechanism of action (cytotoxicity): Methotrexate enters the cell via a specific folate carrier protein and MTX binds reversibly to DHFR.

MTX and folic acid are polyglutamated by folylpolyglutamate synthetase. The polyglutamated forms are retained within cancer cells producing increased inhibitory effects on enzymes involved in purine synthesis and thymidylate synthesis.

Upon cell exposure to MTX, dihydrofolate accumulates and tetrahydrofolate declines. Tetrahydrofolates serve as one carbon donors in the synthesis of purine rings.

Tetrahydrofolate (leucovorin, citrovorum factor) is the product of the blocked reaction. Tetrahydrofolate can rescue the cell, neoplastic or normal, from the cytotoxicity of MTX.

Selectivity of leucovorin rescue may depend on the extent of polyglutamation of MTX in normal and malignant cells. Bone marrow cells and intestinal epithelial cells do not form appreciable levels of MTX-polyglutamate and leucovorin can “Rescue” these cells.

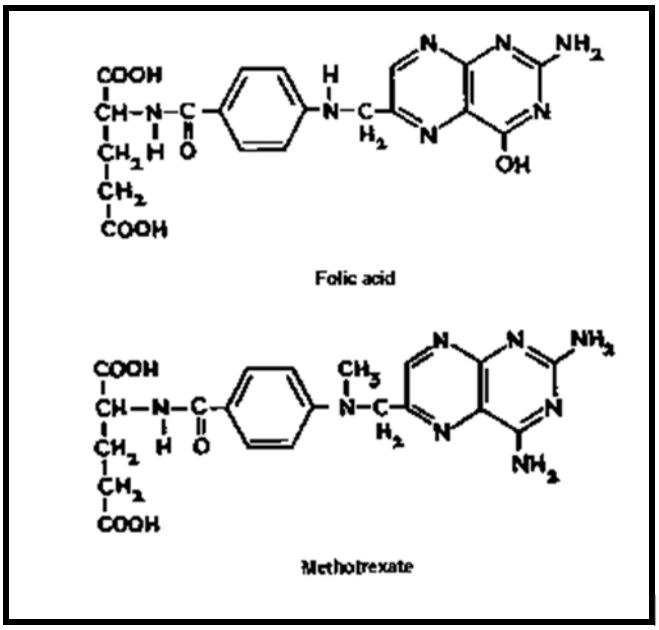

Figure 1. A comparison of folic acid and methotrexate. Original citation not available. K. Micetich, M.D.

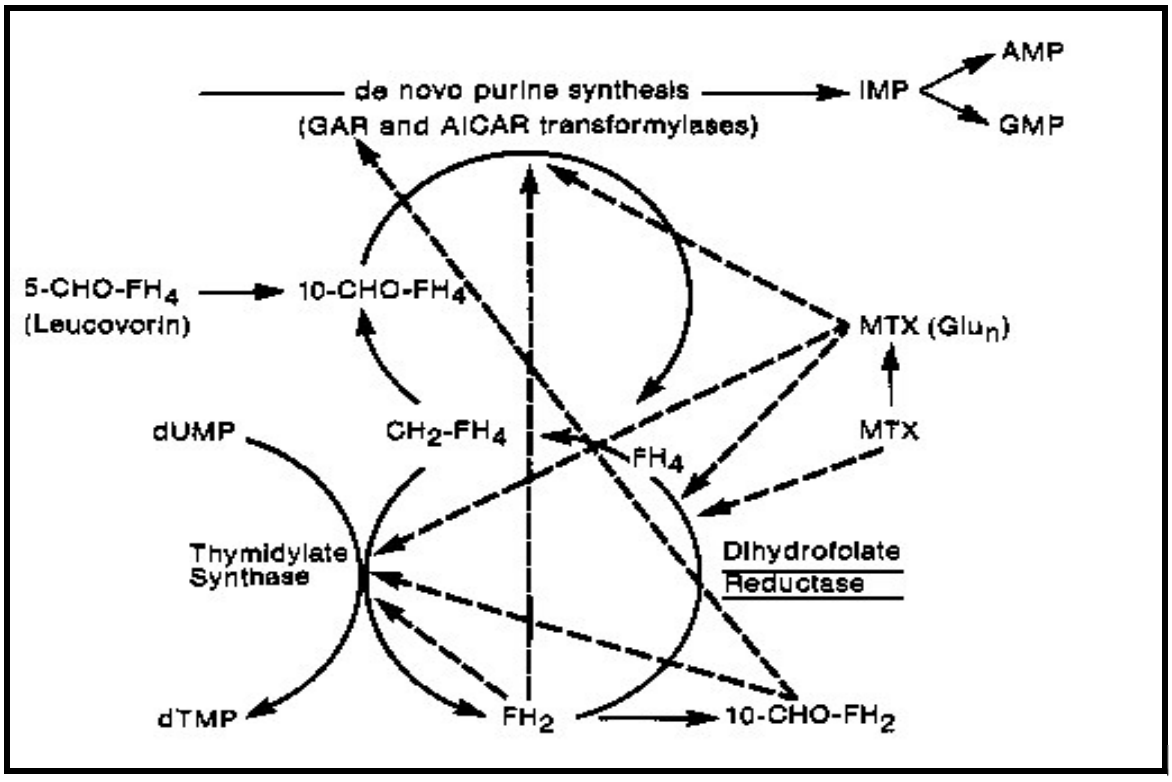

Figure 2. The mechanism of action of methotrexate. Original citation not available. K. Micetich, M.D.

f) Pharmacokinetics and metabolism: The drug is yellow in solution. It is metabolized in the body and excreted in the urine.

Characteristics of MTX have profound clinical impact and these are listed below:

CHARACTERISTIC	CLINICAL IMPLICATION
1. Protein bound	Co-administered drugs which displace MTX from albumin binding sites may potentiate toxicity (Aspirin, sulfonamides, penicillins).
2. Volume of distribution is total body water	MTX gains access to third space accumulations of fluid and will slowly leak out and cause a prolonged tail of excretion: ascites and pleural effusions are relative contraindications to the drug.
3. MTX is filtered, secreted and reabsorbed by the kidney.	Use with caution in patients with impaired renal function.
4. MTX is excreted by the kidney as the salt of a weak acid.	Aspirin, penicillins are also excreted in this way. Therefore, these drugs will interfere with urinary excretion of MTX. Probenecid blocks the organic acid transport system and will also interfere with excretion.
5. MTX solubility markedly increases in alkaline pH. Solubility at pH=5 is 0.39 mg/ml; pH=6 is 1.55 mg/ml and at pH=7 is 9.04 mg/ml.	Alkalinize excretion to promote excretion.
6. Penetrates the central nervous system (CNS) when given in high doses.	High intravenous doses may provide protection to CNS against spread to tumor.

g) Side effects (toxicity): Mild nausea and vomiting, stomatitis, myelosuppression is dose limiting.

h) Special features and dose modifications:

(1) the drug is approved for intrathecal administration and is used to treat carcinomatous or lymphomatous meningitis.

(2) The dose of drug must be reduced in the presence of renal insufficiency

(3) High dose methotrexate (1-10 gm/M2) with leucovorin rescue.

a. Intravenous hydration with sodium bicarbonate to alkalinize urine
b. Check urine pH each void. Do not administer methotrexate unless pH >=7.
c. Administer methotrexate intravenously.
d. Variable time period later begin intravenous or oral leucovorin administration
e. Monitor methotrexate levels.
f. Stop rescue when methotrexate level is $< 5 \times 10^{-7}$ M at 48 hours

Potential success requires neoplastic cell sensitivity to having DNA synthesis turned off.

Tetrahydrofolate is the rescue. If cells have poly-glutamated MTX, leucovorin probably will not rescue. Bone marrow cells and gastrointestinal epithelial cells do not form polyglutamates. Therefore, bone marrow and GI epithelium is rescued.

Toxicity of high dose therapy is NOT myelosuppression. The following may occur: stomatitis, enteritis, conjunctivitis, renal failure and rarely, hepatic failure.

i) Uses: Breast cancer, leukemia, lymphoma, brain tumors, rheumatoid arthritis, and psoriasis. The use of methotrexate to treat female choriocarcinoma is the first time that a cancer was cured using chemotherapy.
Other compounds in this class: Antifolate: pemetrexed. This drug is classified as antifolate since it disrupts folate dependent metabolic processes. The drug is transported into the cell via a folate carrier and is polyglutamated. It inhibits thymidylate synthesis. The drug is useful in the treatment of lung cancer and mesothelioma. Myelosuppression is dose limiting. Also noted is rash, stomatitis and diarrhea. Hand-foot syndrome may occur. Pretreatment with parenteral vitamin B-12 and oral folic acid decreases the extent of myelosuppression.

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b) Pyrimidine antagonist: Cytarabine (cytosine arabinoside).

a) Name, class: Cytarabine, antimetabolite.
b) Cycle specificity: CSS (S phase).
c) Macromolecular target: DNA.
d) Bioactivation if necessary: Successive phosphorylation via kinases to the triphosphate.
e) Mechanism of action (cytotoxicity): Cytosine arabinoside is taken up in the cell via a carrier mediated nucleoside transport mechanism and converted to the triphosphate via kinases. The ARA-CTP triphosphate is the main cytotoxic metabolite. Ara-CTP inhibits DNA polymerase. Ara-CTP is incorporated into DNA and inhibits template function and chain elongation. The cytotoxicity is related to the duration of exposure of the cell to Ara-C (cytosine arabinoside). Specifically, the retention of Ara-CTP at 4 hours is predictive of cancer cell kill.

f) Pharmacokinetics and metabolism: The initial half-life of cytosine arabinoside is 7-20 minutes and the terminal half-life is about 2 hours. Since there is an S phase specificity and since the half-life is short, the drug exhibits schedule dependent cytotoxicity.

The drug is metabolized by a ubiquitous deaminase.

g) Side effects (toxicity): Nausea and vomiting, hair loss, hepatic toxicity, stomatitis, and myelosuppression (dose limiting).

h) Special features and dose modifications:

(1) the drug is approved for intrathecal use for the treatment of carcinomatous or lymphomatous meningitis.

(2) HIDAC (high dose ara-c) therapy: cytarabine (2-3 gm./M2) intravenously every 12 hours for 6 to 12 doses. Toxicity is myelosuppression and cerebellar toxicity and conjunctivitis (steroid eye drops help prevent chemo conjunctivitis).

i) Uses: Cytarabine is used exclusively in the treatment of acute leukemia. It is used in the 3 + 7 inducation regimen: an anthracycline administered intravenously for 3 days and a continuous intravenous infusion of cytarabine (100-200 mg/M2/day) for 7 days. The continuous infusion takes advantage of the schedule dependent cytotoxicitiy of this drug.

j) Other compounds in this class: gemcitabine. Mechanism of action similar to cytosine arabinoside. Myelosuppression is dose limiting. Useful in the palliative treatment of cancer of the pancreas and lung cancer.

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c) Fluorinated pyrimidine: 5-Fluorouracil

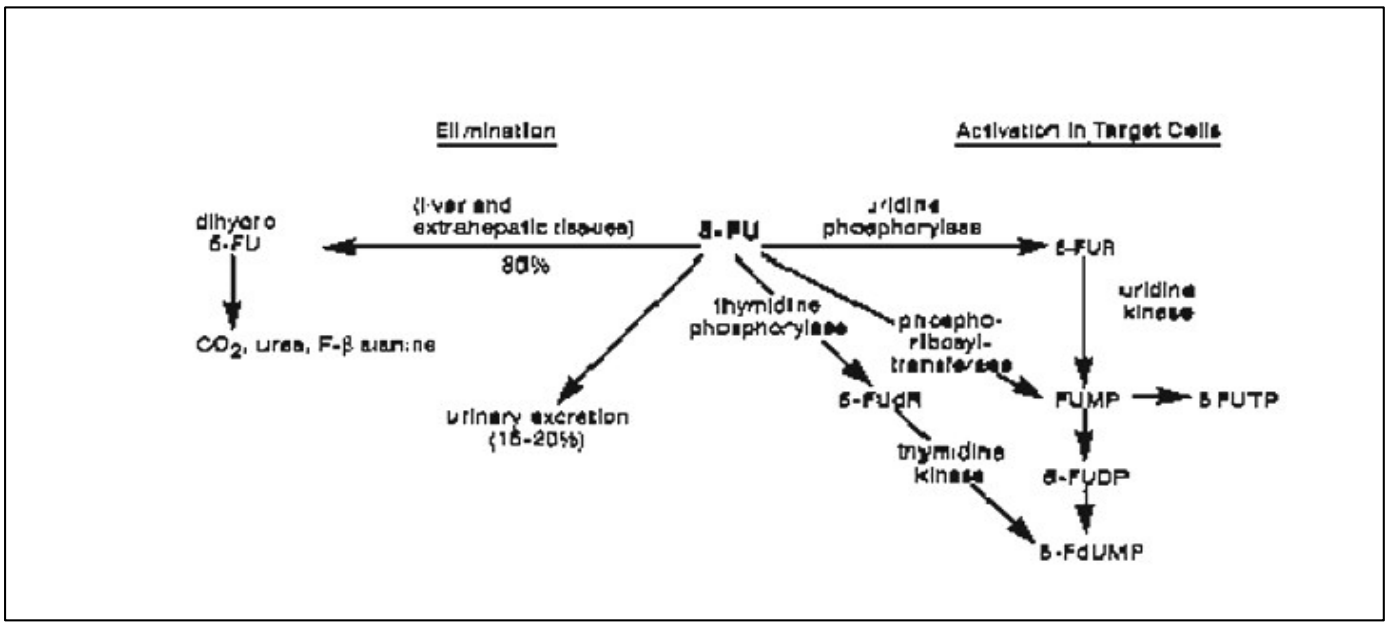
a) Name, class: 5-fluorouracil, antimetabolite.

b) Cycle specificity: CCS (S-phase).

c) Macromolecular target: Thymidylate synthetase, RNA and DNA.

d) Bioactivation if necessary: Successive phosphorylation to the triphosphate and metabolism to FdUMP.

e) Mechanism of action (cytotoxicity): (1) Production of FdUMP which inhibits thymidylate synthetase. Tetrahydrofolate + FdUMP binds tightly to thymidylate synthetase and decreases the production of thymine nucleotides (thymineless death). (2) Sequential phosphorylation and incorporation into the RNA and DNA.



Metabolism and bioactivation of 5-FU. Original citation not available. K. Micetich, M.D.

f) Pharmacokinetics and metabolism: Extensively metabolized by the liver.

g) Side effects (toxicity): Standard doses: rash, stomatitis and diarrhea and mild myelosuppression. Hyperpigmentation of the skin occurs and there is an increased sensitivity to sunlight. Chest pain (due to coronary artery vasospasm) and cerebellar ataxia rarely occur. Excess lacrimation. Hand foot syndrome.

h) Special features and dose modifications:

(1) some feel that the efficacy of the drug is better when given as an infusion (short half-life and cell-cycle specific) rather than as bolus administration (rapid intravenous push).

(2) 5-FU is frequently given concomitantly with radiation therapy as a radiation sensitizer.

(3) 5-FU plus leucovorin is better than 5-FU alone. The response rates are better but stomatitis and diarrhea are worse. Leucovorin potentiates the cytotoxicity of 5-FU.

(4) Initial metabolism requires dihydropyrimidine dehydrogenase (DPD). 3-5 % of the population is deficient (autosomal recessive inheritance). Severe toxicity results when these patients are treated with 5-FU.

(5) There are several schedules of administration in use. There are differing toxicity profiles depending on the schedule of administration.

i) Uses: Breast cancer, head and neck cancer, gastrointestinal cancers.

j) Other compounds in this class: Capecitabine. Prodrug of 5-FU. Metabolized in the liver by carboxylesterase to an intermediate, then converted by cytadine deaminase to 5'deoxy-5fluorouradine. This is then hydrolyzed by thymidine phosphorylase to fluorouracil in the tumor. Tumor cells have higher concentrations then normal cells of thymidine phosphrylase. This is an oral chemotherapy drug. Useful in gastrointestinal tract malignancies and breast cancer. Side effects include: rash, hand foot syndrome, diarrhea. Myelsuppression can occur as well. Capecitabine can replace intravenous 5-FU infusions.

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d) Purine antagonist: 6-mercaptopurine.

a) Name, class: 6-mercaptopurine, antimetabolite.
b) Cycle specificity: CSS (S phase).
c) Macromolecular target: Enzyme inhibition and incorporation into RNA and DNA
d) Bioactivation if necessary: Metabolized by hypoxanthine-guanine phophoribosyl transferase to form 6-thioinosinic acid.
e) Mechanism of action (cytotoxicity): 6-thioinosinic acid inhibits enzymes of de novo purine nucleotide synthesis.
f) Pharmacokinetics and metabolism: 6-mecaptopurine is metabolized to inactive 6-thiouric acid by the enzyme xanthine oxidase.
g) Side effects (toxicity): myelosuppression (dose limiting).
h) Special features and dose modifications: The dose of this drug must be reduced 50-75 % when given with allopurinol.
i) Uses: Childhood acute leukemia
j) Other compounds in this class: 6-thioguanine. 6-thioguanine undergoes a deamination during its metabolism and there is no interaction with xanthine oxidase. 6-thioguanine can be used at full doses with allopurinol.

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3. REVIEW QUESTIONS:

1. Discuss the activation of and the mechanism of action of 5-FU and cytarabine.

2. Leucovorin is the rescue for methotrexate but potentiates the cytotoxicity and toxicity of 5-FU. Explain the mechanisms of rescue of methotrexate and the potentiation of 5-FU by leucovorin.

3. When 6-mercaptopurine is administered to a patient who is on allopurinol, should the dose of 6-mercaptopurine be modified? Why or why not.

4. 100 mg/M2/day of cytosine arabinoside given as a 24 hour continuous intravenous infusion in the 3 + 7 regimen is better than cytosine arabinoside given as a rapid bolus injection in the same regimen. Why? What is this an example of?

5. A 42 year old male is receiving treatment for Lymphoma with high dose methotrexate. The intern administers 5 grams of methotrexate over 6 hours and sends the patient home. The attending insists that the patient be readmitted and tells the intern to give the rescue intravenously. The intern writes for the patient to receive 50 mg of folic acid intravenously every 6 hours for 8 doses. Is this correct? What is wrong?

6. Polyglutamation of methotrexate decreases the ability of leucovorin to rescue any cell from the cytotoxicity of methotrexate. Why?

7. Indicate why each of the following is a contraindication to administration of methotrexate:

    a) pleural effusion or ascites;

    b) renal failure;

    c) concomitant treatment with the uricosuric agent, probenecid.

8. Name two chemotherapeutic agents approved for intrathecal administration.

9. Why is alkalinization of the urine important in the implementation of the high dose methotrexate with rescue strategy?

CHEMOTHERAPY V: Targeted Cancer Therapies and miscellaneous agents

Date: April 14, 2014 – 9:30 AM
Reading Assignment: Katzung: pp. 966-969

Suggested:

Chabner B. Early accelerated approval for highly targeted cancer drugs. New Engl J Med 2011; 364: 1087-1089

Krause D.S., Van Etten R.A. Tyrosine kinases as targets for cancer therapy. New Engl J Med 2005; 353:172-187.

Kerbel R.S. Tumor angiogenesis. New Engl J Med 2008; 358:2039-2049.

Ciardello F, Tortora G. EGFR antagonists in cancer treatment. New Engl J Med 2008; 358:1160-1174.

Flaherty K.T., Puzanov I. et al. Inhibition of mutated, activated BRAF in metastatic melanoma. New Engl J Med 2010; 363:809-819.

Kwak E.L., Bang Y.J., et al. Anaplastic lymphoma kinase inhibition in non-small cell lung cancer. New Engl J Med 2010; 363: 1693-1703.

KEY CONCEPTS & LEARNING OBJECTIVES

1. Define targeted therapy
2. Describe the mechanism of action of imatinib mesylate and list the indications for the use of this drug.
3. Describe the mechanism of action and side effects of cetuximab
4. Describe the mechanism of action and side effects of bevacizumab
5. Describe the mechanism of action and side effects of trastuzumab
6. List the indication(s) for treatment with cetuximab, bevacizumab, trastuzumab and erlotinib.
7. State the indication for treatment of a patient with all-transretinoic acid.
8. Indicate the mechanism of action of Asparaginase
9. State the indication for treatment of a patient with asparaginase.

DRUGS COVERED IN THE LECTURE

1. Imatinib mesylate
2. Cetuximab

Received: 4/3/14

Pharmacology & Therapeutics Chemotherapy V: Targeted Cancer Therapies and miscellaneous agents
April 14, 2014 Kenneth C. Micetich, M.D.

3. Erlotinib
4. Bevacizumab
5. Trastuzumab
6. Sorafenib
7. Sunitinib
8. Pazobanib
9. L-asparaginase
10. Hydroxyurea
11. All-trans-retinoic acid
12. Arsenic trioxide

Received: 4/3/14

CHEMOTHERAPY V: TARGETED THERAPIES OF CANCER MISCELLANEOUS AGENTS

TARGETED THERAPIES OF CANCER

Targeted cancer therapy:

The term "targeted therapy" refers to a new generation of cancer drugs designed to interfere with a specific molecular target (typically a protein) that is believed to have a critical role in tumor growth or progression. The identification of appropriate targets is based on a detailed understanding of the molecular changes underlying cancer. This approach contrasts with the conventional, more empirical approach used to develop cytotoxic chemotherapeutics -- the mainstay of cancer drug development in past decades. (Charles Sawyers Nature 2004 432:294).

The main target is a tyrosine kinase. Pharmacologic inhibition of a tyrosine kinase can be achieved by (1) small molecule inhibition of the catalytic activity of the kinase or (2) antibodies against the receptor tyrosine kinases or a ligand of the receptor tyrosine kinase. Some drugs inhibit a specific tyrosine kinase while others may target multiple tyrosine kinases.

Genomics has the potential to identify critical signaling pathways in a cancer. In turn pharmacologic strategies can be developed to inhibit the pathways (personalized medicine).

The traditional method of drug development may not be applicable to tyrosine kinase inhibitors. The toxicities can be low and the therapeutic responses may be limited to a small group of patients. Patients participating in these projects should be selected based on the identification of a particular activating pathway.

a) Imatinib mesylate

a) Name, class: Imatinib mesylate (tyrosine kinase inhibitor)
b) Cycle specificity: N/A
c) Macromolecular target: Bcr-Abl fusion protein; c-kit
d) Bioactivation if necessary: N/A
e) Mechanism of action (cytotoxicity): Inhibits critical signaling pathways in the cancer cell that are constitutively active.
f) Pharmacokinetics and metabolism: Metabolized in the liver by the CYP3A4 system and excreted into the feces by the hepatobiliary system.
g) Side effects (toxicity): Superficial edema, nausea, muscle cramps, abdominal pain, musculoskeletal pain, rash, diarrhea, anemia, neutropenia, thrombocytopenia. Rarely, congestive heart failure.
h) Special features and dose modifications: Drug is given orally.

(1) Monitor thyroid function (TSH levels) in hypothyroid patients who are taking thyroid replacement therapy. Imatinib may increase the clearance of thyroid hormone and the dose of thyroid medication may have to be increased.

(2) Metabolized by CYP3A4 system. Avoid coadministration with inducers (St. John's Wort) and inhibitors of the pathway-other drugs and grapefruit juice

i) Uses: Chronic myelogenous leukemia; Gastrointestinal stromal tumor.
j) Other compounds in this class: Dasatinib and nilotinib (useful in imatinib resistant disease)

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b) Cetuximab

a) Name, class: Cetuximab, epidermal growth factor receptor (EGFR) inhibitor **b)**
Cycle specificity: N/A
c) Macromolecular target: EGFR
d) Bioactivation if necessary: N/A
e) Mechanism of action (cytotoxicity): Overexpression of EGFR receptors leads to increased signaling and affects cell growth and division and metastases and invasion. Also can sensitize cell to effect of chemotherapy and can be used as a radiation therapy sensitizer. **f) Pharmacokinetics and metabolism:** N/A
g) Side effects (toxicity): Hypersensitivity reactions; rash; diarrhea, hypomagnesemia
h) Special features and dose modifications: Drug is a chimeric monoclonal antibody administered inravenously weekly or every other week usually in combination with chemotherapy.
i) Uses:

(1) Lung cancer and head and neck cancer (patients not selected on basis of EGFR expression)

(2) Colo-rectal cancer (metastatic); perform k-ras mutational analysis on rumor. If k-ras is wildtype patient may respond to cetuximab; If k-ras is mutated, patient will not respond to cetuximab.

j) Other compounds in this class: Panitumumab (fully humanized monoclonal antibody)

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c) erlotinib

a) Name, class: erlotinib, small molecule inhibitor of the tyrosine kinase domain associated with EGFR
b) Cycle specificity: N/A
c) Macromolecular target: Tyrosine kinase domain associated with EGFR
d) Bioactivation if necessary: N/A
e) Mechanism of action (cytotoxicity): Inhibition of critical cell signaling pathways.
f) Pharmacokinetics and metabolism: Metabolized by CYP3A4. Avoid coadministration with inducers (St. John's Wort) and inhibitors of the pathway-other drugs and grapefruit juice.

g) Side effects (toxicity): Rash, nausea, anorexia and fatigue.
h) Special features and dose modifications: Oral administration

(1) Metabolized by CYP3A4. Avoid coadministration with inducers (St. John's Wort) and inhibitors of the pathway-other drugs and grapefruit juice.

(2) Patients with non-small cell lung cancer should have mutational analysis done on the tumor. There are activating mutations observed. If the patient has an activating mutation, the treatment of choice in a patient with metastatic disease is erlotinib and is superior to chemotherapy.
i) Uses: Lung cancer, head and neck cancer, pancreas cancer (in combination with gemcitabine)
j) Other compounds in this class: None commercially available.

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d) bevacizumab

a) Name, class: bevacizumab, inhibitor of vascular endothelial growth factor (VEGF) **b) Cycle specificity:** N/A
c) Macromolecular target: vascular endothelial growth factor ligand
d) Bioactivation if necessary: N/A
e) Mechanism of action (cytotoxicity): The monoclonal antibody binds to VEGF ligand and presumably decreases the growth of primary cancers and metastatic cancers due to impaired vasculature formation in the tumor.
f) Pharmacokinetics and metabolism: N/A
g) Side effects (toxicity): Infusion reactions, proteinuria, hypertension, arterial clots, bleeding, perforation of the colon, reversible posterior leukoencephalopathy syndrome is rare (seizures, headache, mental status changes, visual changes and findings on MR of the brain) **h) Special features and dose modifications:** Intravenous administration.
i) Uses: Lung cancer and metastatic colorectal cancer.
j) Other compounds in this class: Sorafenib, pazopanib, and sunitinib are small molecule inhibitors of vegf receptor tyrosine kinases. These drugs are available orally. Side effects include rash, hand-foot syndrome. They can cause hypertension, reversible posterior leukoencephalopathy syndrome, and perforation of the gastrointestinal tract. Congestive heart failure has been reported.

All three drugs are useful in renal cell cancer (clear cell variety). Sorafenib has efficacy in hepatocellular cancer. Sunitinib has utility in the treatment of pancreatic neuroendocrine cancer and GI stromal tumors.

The small molecule VEGF receptor tyrosine kinase inhibitors are all metabolized by the CYP3A4 system.

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e) trastuzumab

a) Name, class: Trastuzumab, monoclonal antibody.
b) Cycle specificity: N/A
c) Macromolecular target: Extracellular domain of epidermal growth factor receptor, her-2/neu
d) Bioactivation if necessary: N/A
e) Mechanism of action (cytotoxicity): Trastuzumab binds to the extracellular domain of the epidermal growth factor receptor and decreases signaling pathways. **f) Pharmacokinetics and metabolism:** N/A
g) Side effects (toxicity):

(1) The most common side effects associated with traztusumab were fever, nausea, vomiting, infusion reactions, diarrhea, cough, headache, fatigue, shortness of breath, back pain, rash, and muscle pain. Allergic reactions have also been reported.
(2) Heart failure [The risk of heart problems was higher in people who received both trastuzumab and doxorubicin]. Patients receiving trastuzumab should be evaluated before and frequently monitored throughout treatment for any ddecline in the cardiac ejection fraction. rop in heart function. Patients with pre-existing heart problems should be monitored more frequently. The heart failure seen with trastuzumab differs from that observed with the anthracyclines: it is usually manifested as an asymptomatic decline in the ejection fraction, and is not cumulative. Overt congestive heart failure is rare. The decline in the ejection fraction is reversible and the patient can be rechallenged with the drug.

h) Special features and dose modifications: Drug is a monoclonal antibody administered intravenously weekly.
i) Uses: Breast cancer in combination with chemotherapy when the breast cancer overexpresses Her-2/neu. Stomach and gastroesophageal junction cancer in combination with chemotherapy when the cancer overexpresses Her-2/neu.
j) Other compounds in this class: lapatinib (small molecule tyrosine kinase inhibitor of her-2 family; pertuzumab (monoclonal antibody binds to Her-2).

MISCELLANEOUS AGENTS:

Asparaginase. The drug is a bacterial product and hydrolyzes L-asparagine. Tumor cells lack asparagine synthetase and protein synthesis is inhibited. Toxicities are due to immunologic sensitization and depletion of asparagine pools. Allergic reactions can occur; clotting and bleeding (concentration of clotting factors and antithrombin III decrease), pancreatitis, hyperglycemia and mental status changes. Liver enzyme abnormalities occur in all patients. Useful in treatment of acute lymphocytic leukemia.

Hydroxyurea. Analog of urea that inhibits DNA synthesis by inhibiting ribonucleotide reductase. Drug is administered orally. Main use is in treatment of high white blood cell counts in patients with acute myelogenous leukemia and chronic granulocytic leukemia with blast crisis. The leukemic blasts in high numbers can cause sludging in the vasculature leading to thromboses. Once the count is controlled other treatments can be given. Toxicity includes nausea and vomiting, low blood counts and rash.

All-trans-retinoic acid (tretinoin). Treatment of choice in combination with chemotherapy for patients with acute promyelocytic leukemia (APL, M3). The drug induces terminal differentiation of the leukemic cells. Side effects: dry skin and dry

mucus membranes. Retinoic acid syndrome consisting of fever, weight gain, pulmonary infiltrates and pleural or pericardial effusions.

Arsenic Trioxide. Used in the treatment of APL. Side effects include fatigue, QT prolongation and a syndrome similar to the retinoic acid syndrome (see tretinoin).

CHEMOTHERAPY VI:
PRINCIPLES OF CANCER TREATMENT

Date: April 15, 2014 – 8:30 am

Reading Assignment: Katzung: pp. 949-951; 969-974

KEY CONCEPTS & LEARNING OBJECTIVES

1. State the goals of the treatment of the cancer patient with chemotherapy.
2. List the chemocurable cancers
3. Define adjuvant and neoadjuvant therapy
4. Define performance status
5. List the rules for creating a combination chemotherapy drug program
6. Indicate why combination chemotherapy is more effective than treatment with a single agent.
7. Recognize when chemotherapy is being given in the adjuvant setting, the neoadjuvant setting and the advanced disease setting.
8. State the rationale for the administration of adjuvant chemotherapy
9. State the single cause of the failure of chemotherapy to cure a patient with cancer.

CHEMOTHERAPY VI:
PRINCIPLES OF CANCER TREATMENT

1. GENERAL PRINCIPLES OF TREATMENT.

a) Establish the diagnosis: Biopsy (cytology, excisional, incisional). There is no test short of a biopsy that can establish the diagnosis although the diagnosis may be strongly suspected prior to the definitive biopsy (see appendix 1). The pathology report may also include information that is predictive of a response or non-response to a particular chemotherapy drug.

b) Determine the stage: The stage of a cancer is a uniform system that physicians use which indicates extent of disease at the time of diagnosis. Commonly used staging tests are physical examination, blood tests and imaging modalities such as x-rays and CT scans.

T-primary tumor (size, depth of penetration into the wall of an organ)
N-number of regional nodes involved
M-presence or absence of metastatic disease

TNM classification and stage of the cancer (1,2,3,4).

c) Determine the prognosis and treatment: Stage determines prognosis and treatment. In general:

1) cancer confined to the organ of origin
2) cancer confined to the organ of origin with spread to the regional draining lymph nodes
3) metastatic disease

Cancers localized to the organ of origin are treated with local therapies: surgery/radiation therapy.

The prognosis as a function of stage:

Localized disease>local-regional disease>disseminated disease

Cancers which are metastatic at the time of diagnosis or cancers associated with a high chance of having micrometastases (high recurrence rate after the removal of the primary tumor) require a systemic, blood-borne therapy.

d) Educate the patient about the prognosis and the treatment.

e) Clearly define the goals of any therapy (curative/palliative) and clearly define the expectation of benefit for the patient and indicate how the patient will monitored and disease response assessed. Use regimens that have been published in the literature and are accepted by the oncology community. Have a plan for monitoring response.

f) Evaluate the patient to make certain that the patient can tolerate the potential side effects of any treatment.

2. CHEMOTHERAPY

Chemotherapy (a systemic therapy) are drugs given orally or parenterally in an attempt to control or to eradicate a malignant process.

Chemotherapy is given to patients

(a) who have had a cancer removed but who are believed to be at risk of having micrometastatic disease (adjuvant chemotherapy);

(b) with curative or palliative intent who have clinically apparent metastatic (advanced, metastatic) disease;

(c) with a large tumor burden to achieve cytoreduction prior to surgery (neoadjuvant chemotherapy).

(d) to prevent a cancer.

TOLERANCE OF CHEMOTHERAPY

- Patient performance status (0-5):
- 0-fully active
- 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work •
  2-Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3-Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4-Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- 5-Death
- End organ function
- Requires knowledge of efficacy of treatments, drugs to be used, known side effects and pharmacology

3. LOG KILL HYPOTHESIS

The killing of cancer cells by the chemotherapy drugs follows first order kinetics. The same fraction of cancer cells is killed with each administration of chemotherapy.

Thus, in order to achieve a cure with chemotherapy, multiple courses of chemotherapy will have to be given.

Hypothetical example: Assume no resistant cells and a fractional cell kill of 99 % (two log cell kill) with each administration of chemotherapy and assume an initial tumor burden to 1 X 1012 cells.

Table 1. Hypothetical example

CELL NUMBER (Before each cycle)	CELL NUMBER (After each cycle)
1012	1010
1010	108
108	106
106	104
104	102
102	100

Note that tumor regrowth in between cycles of chemotherapy may occur.

4. SINGLE AGENT VS. COMBINATION CHEMOTHERAPY

- The treatment of cancers with single drugs was unable to produce significant remissions or cures.

- Combination chemotherapy or the treatment of cancers with two or more agents was able to produce significant remissions or cures.

- Drug combinations are more effective than single agents because:

- they provide maximal cell kill within the range of toxicity tolerated by the host for each drug (fractional cell kill or log cell kill is increased in combinations compared to single agents);

- combining drugs with different mechanisms of action provides a broader range of coverage of de novo resistant cell lines. This is very important: **Our ability to cure cancers is due to chemoresistant cancer cells.**

5. HOW TO CREATE A COMBINATION?

RULES

(1) Drugs chosen for the combination should possess activity against the disease when utilized as a single agent (determined from phase II studies).

(2) The drugs chosen should have non-overlapping toxicities (except for hair loss and myelosuppression, nausea and vomiting.

(3) Combine drugs with different mechanisms of action.

(4) Combine cell cycle specific and cell cycle non-specific drugs.

(5) Drugs should be given in an optimal dose and an optimal schedule. A dose response relationship exists between response rate and dose of chemotherapy administered.

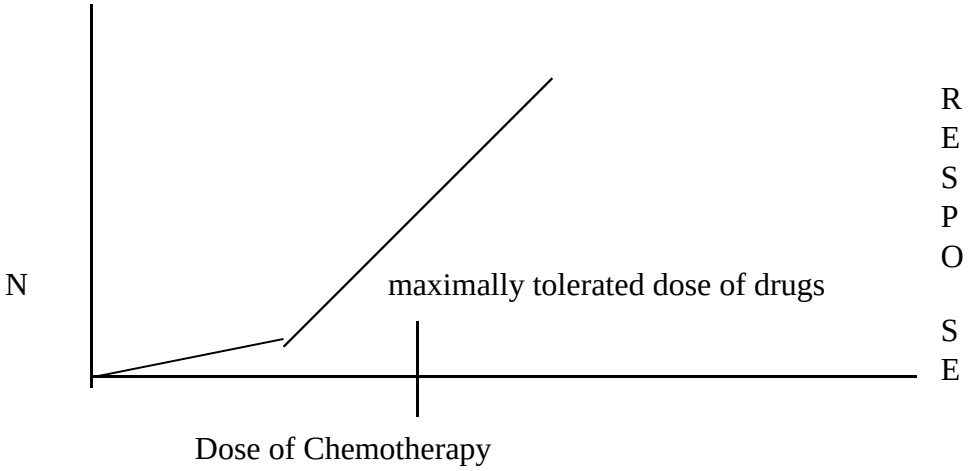


Figure 1. Dose response curve to chemotherapy Original citation not available. K. Micetich, M.D.

The dose response curve also provides the rationale for high dose intensive therapy (bone marrow transplantation.

6. ADJUVANT CHEMOTHERAPY

Table 1. Breast Cancer stage (post surgical) and 10 Year Survival.

Breast Cancer Stage	10 year Survival
T1N0M0 (Stage 1)	82 %
T1N1M0 (Stage 2)	40 %
Metastatic disease (M +) (stage 4)	<20 %

Table 2. Lung Cancer Stage (post surgical) and 5 Year Survival.

Lung Cancer Stage	5 year Survival
T1N0M0 (Stage 1)	60 %
T1N1M0 (Stage 2)	30 %
Metastatic disease (M +) (stage 4)	0 %

For discussion:

a) How is it possible that a patient can have a cancer removed as in the stage 1 and stage 2 breast and lung cancers presented in the above table, and develop metastatic disease at a later time?

b) Indicate how the Goldie-Coldman hypothesis supports the administration of chemotherapy to patients who have had a cancer removed but are at risk of recurrence at a later date.

Adjuvant therapy after surgery is indicated in the following situations:

1. **node positive and selected node negative breast cancers**
2. **stomach cancer**
3. **pancreas cancer**
4. **selected patients with melanoma**
5. **node positive colon and rectal cancers**
6. **osteogenic sarcoma**
7. **lung cancer**
8. **testicular cancer**

7. CHEMOTHERAPY FOR METASTATIC DISEASE

a) a particular regimen is chosen which has been shown to improve overall survival
b) the patient has measureable or evaluable disease on imaging
c) a certain number of cycles is given and then the patient is reimaged

a. stable disease, partial remission or complete remission→continue therapy for a certain number of cycles. Patient must be able to tolerate the therapy.
b. If progression of disease, then chemoresistance is present and the regimen is changed if appropriate

d) At some point, the patient's cancer becomes resistant to all the drugs and the patient gets progressively weaker and palliative, hospice care is appropriate.

Useful information:

www.cancer.gov -Official site of the National Cancer Institute. Contains A wealth of information for all cancers (staging and treatment according to stage; prevention and screening).

www.adjuvantonline.com –this site helps health professionals and patients with early cancer discuss the risks and benefits of getting additional adjuvant therapy after surgery. Computer program indicates the survival (overall and disease free) with and without adjuvant therapy for breast, lung and colon cancers.

www.nccn.org: National Comprehensive Cancer Network. Practice guidelines for the treatment and care of the patient with cancer for most cancer sites.

AJCC Cancer Staging Manual, 7th Edition, 2010

An important oncology textbook is:

Principles and Practice of Oncology. DeVita, Hellman, and Rosenberg. 9th Edition. April, 2011.

7. REVIEW QUESTIONS:

1. What is the stage of a cancer, how is it determined and what is its significance?

2. Why is treatment with combination chemotherapy more effective than chemotherapy with single agents?

3. List the rules for creating a combination chemotherapy regimen.

4. Define adjuvant chemotherapy.

5. Why is adjuvant therapy effective in some but not all patients?

6. Indicate which of the following are potentially chemocurable:

    a) Advanced stage Hodgkin's disease
    b) Advanced stage testicular cancer
    c) Advanced stage non Hodgkin's lymphoma (aggressive)
    d) Metastatic colon cancer
    e) Metastatic breast cancer
    f) Some childhood leukemias

APPENDIX 1.

Pathology report of a patient with colon cancer.

FINAL DIAGNOSIS
A. COLON, RIGHT; RESECTION: (SPECIMEN A)
-INVASIVE ADENOCARCINOMA, MODERATE TO POORLY DIFFERENTIATED (SIZE 9.0 CM),
TUMOR EXTENDS THROUGH THE MUSCULARIS PROPRIA INTO THE SUB-SEROSAL ADIPOSE TISSUE AND INVOLVES THE SEROSAL SURFACE
-PERINEURAL AND PERIVASCULAR INVASION IS PRESENT
-PROXIMAL AND DISTAL MARGINS NEGATIVE FOR CARCINOMA
-TUMOR IMPLANT IS PRESENT LESS THAN 1MM FROM THE INKED MESENTERIC MARGIN
-THIRTEEN OUT OF TWENTY-SEVEN LYMPH NODES POSITIVE FOR METASTATIC CARCINOMA
(13/27)
-SEE STAGING SUMMARY/COMMENT
.
B. SMALL BOWEL; RESECTION: (SPECIMEN B)
-UNREMARKABLE SMALL BOWEL
-NEGATIVE FOR CARCINOMA
.
C. PORTAL LYMPH NODE; EXCISION: (SPECIMEN C)
-ONE LYMPH NODE, POSITIVE FOR METASTATIC CARCINOMA (1/1)
.
D. LIVER, RIGHT LOBE; PARTIAL LOBECTOMY: (SPECIMEN D)
-POORLY DIFFERENTIATED ADENOCARCINOMA (SIZE 2.7 CM), CONSISTENT WITH METASTASES FROM A COLONIC PRIMARY
-PARENCHYMAL RESECTION MARGIN NEGATIVE FOR CARCINOMA
-CHRONIC HEPATITIS, GRADE 2 AND FIBROSIS, STAGE 2
-EXTENSIVE STEATOSIS WITH FOCAL BALLOON CELL CHANGES, SUGGESTIVE OF STEATOHEPATITIS
-SEE COMMENT

Staging Summary / Comment
SMALL BOWEL, COLORECTAL & ANAL CANCER STAGING SUMMARY

Site.....Right colon
Size.....9.0 X 4.0
X 1.0 cm
Histologic type.....Adenocarcinoma

Mucin%.....<5%
Grade.....Moderately to poorly differentiated
Depth of invasion.....Involves the serosal surface
Adjacent organ involvement.....No
Tumor at free serosal surface.....Present
Tumor perforation.....No
Preexisting polyps.....Not seen
Invasion of stalk.....N/A
Lymphatic/Vascular invasion.....Present
Perineural invasion.....Present
Lymphocytic infiltrate at advancing edge.....Not seen
Margins (Distance from tumor)
Proximal.....Negative
Distal.....Negative
Radial.....Tumor implant is present less than 1mm from the mesenteric resection margin
Other pathology.....N/A
Regional lymph nodes (Metastasis/Total).....13/27
Extranodal extension.....Present
Level (adjacent to tumor vs. along vascular trunk).....Adjacent to tumor
Apical lymph node.....N/A
Mesenteric tumor implants (largest size).....Present (0.6cm)
Ancillary studies.....Immunoperoxidase stains
pTNM.....pT4a, N2b, M1b

Addendum Diagnosis
Molecular Oncology
KRAS Mutation Analysis
Body Site: Right Lobe of Liver

RESULTS: wild-type gene.

INTERPRETATION:
No mutations were identified at codons 12 and 13 of the KRAS gene.

COMMENT:
Mutations in the KRAS gene are reported to be associated with resistance to anti-EGFR monoclonal antibody therapies in patients with colorectal cancer.

.
KRAS mutations occur in 30-50% of colorectal adenocarcinomas.
.
This assay analyzes codons 12 and 13 in exon 2 of the KRAS gene; based on the current literature, approximately 98% of mutations are expected to occur in these codons. The analytical sensitivity of the assay is approximately 10%; thus mutations present in a low percentage of cells may not be detected.

Pathology report for a patient with breast cancer:

FINAL DIAGNOSIS
RIGHT AXILLARY SENTINEL LYMPH NODE #1, EXCISION: (SPECIMEN A)
-ONE LYMPH NODE, NEGATIVE FOR CARCINOMA
- RIGHT BREAST SEGMENT; NEEDLE LOCALIZATION LUMPECTOMY: (SPECIMEN B)
-INFILTRATING CARCINOMA,PREDOMINANTLY LOBULAR WITH FOCAL DUCTAL FEATURES, GRADE II,MEASURING 0.8 CM
DISTANCE TO MARGIN IS LESS THAN 0.1 CM (FINAL POSTERIOR MARGIN IS NEGATIVE IN SPECIMEN D)
-ALL THE OTHER MARGINS ARE NEGATIVE FOR CARCINOMA

Tumor markers on invasive carcinoma:
ER: Positive, 100% (Allred score 8)
PR: Positive, 100% (Allred score 8)
HER-2/neu: Negative, 1+ by IHC (FISH test pending)
Ki67: Favorable (less than 10%)

Pathology report of another patient with colon cancer:

RECTOSIGMOID COLON; LOW ANTERIOR RESECTION: (SPECIMEN C)
-INVASIVE MODERATELY TO POORLY DIFFERENTIATED ADENOCARCINOMA, 3.2 X 2.2 X 0.8
CM, EXTENDING INTO PERICOLIC ADIPOSE TISSUE
-SURGICAL RESECTION MARGINS ARE NEGATIVE
-TWO OF THIRTEEN LYMPH NODES WITH METASTATIC ADENOCARCINOMA (2/13)

THERAPEUTICS OF HIV INFECTION

Date: Thursday, April 17, 2014: 10:30AM-12:30PM **Reading assignment:**

Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. Department of Health and Human Services. Updated as a Living Document on October 30, 2013. Available from the AIDSinfo website. Extensive information concerning treatment options with numerous summary tables.

http://aidsinfo.nih.gov/guidelines/

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe how distinct antiretroviral agent classes target different phases of the HIV replication cycle.

2. List the diagnostic criteria and therapeutic goals for the treatment of HIV infection.

3. For each of the major classes of antiretroviral medications used in the treatment of HIV infection, you should be able to describe:
    a) Mechanism of action
    b) Indications and clinical use
    c) Onset and duration of action
    d) Major adverse effects
    e) Contraindications
    f) Significant drug interactions (if any)

4. Explain the requirement for combination therapy in the treatment of HIV infection, and discuss how co-morbid conditions may require modification of that regimen.

5. List the components of an appropriate antiretroviral regimen for a newly diagnosed patient.

Drugs to be covered in this lecture:

1. NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir
Didanosine
Emtracitabine
Lamivudine
Stavudine Tenofovir

Zidovudine

2. NON-NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine
Efavirenz
Etravirine
Nevirapine
Rilpivirine

3. PROTEASE INHIBITORS

Fosamprenavir
Atazanavir
Darunavir
Indinavir
Lopinavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

4. VIRAL INTEGRASE INHIBITORS

Raltegravir
Elvitegravir (new drug)

5. FUSION INHIBITORS

Enfuvirtide

6. CCR5 ANTAGONISTS

Mariviroc

Therapeutics of HIV infection

I. HIV introduction

A. HIV is a retrovirus that infects and kills a subset of immune cells leading to reduced immune function
   1. HIV is managed as a chronic disease with antiretrovirals and therapy of opportunistic infections.
   2. **ARV** (**A**nti**R**etro**v**iral therapy) doesn't cure or eliminate HIV infection.
   3. HIV targets CD4+ or T-helper lymphocytes, destroying the cells.
   4. CD4+ depletion leads to severe immuno-deficiency.
   5. CD4+ counts below 500 cells/mm^3 associated with opportunistic infections.
   6. periodic CD4 counts of infected patients are performed to assess:
      i. immunologic status ii. risk of opportunistic infections
      iii. need for ARV
      iv. response to ARV

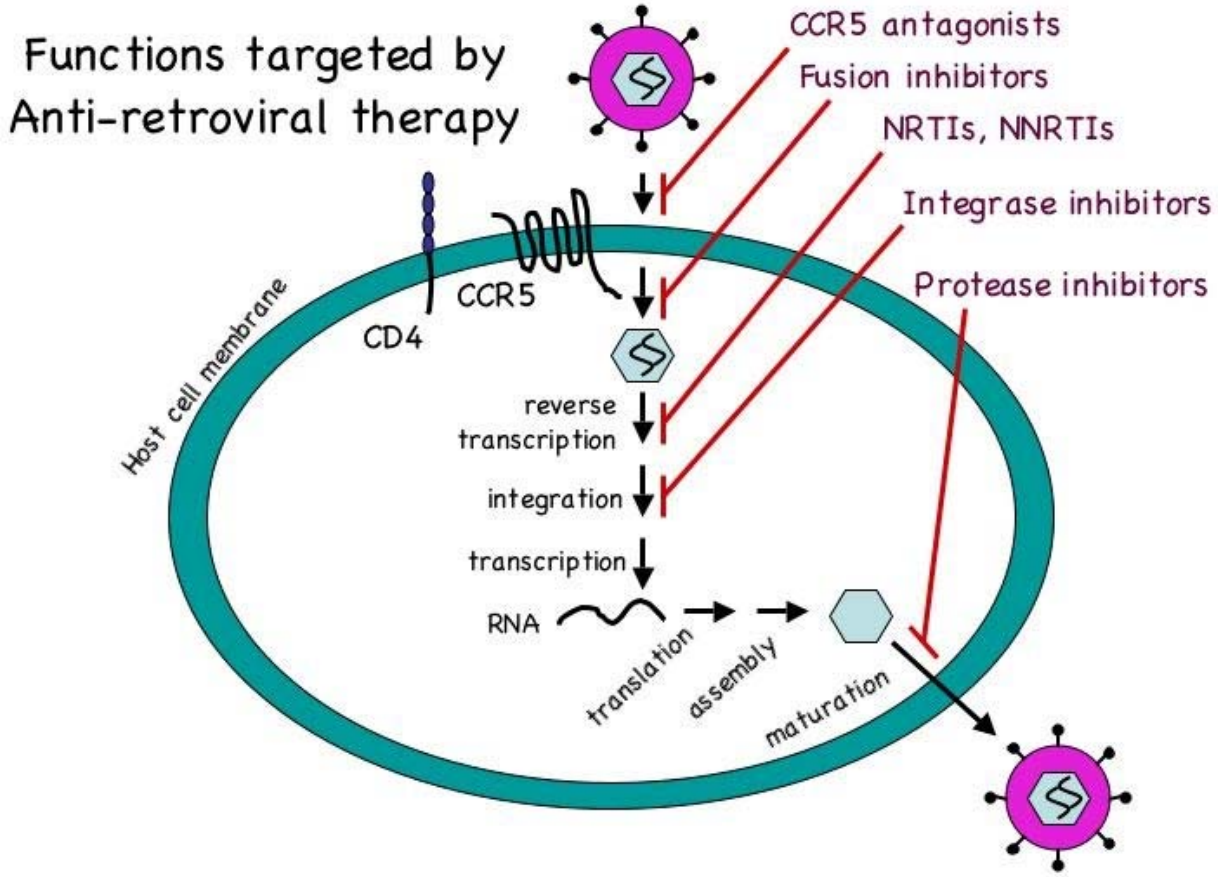
B. Goal of anti-retroviral therapy-reduce viral load and maintain immune function
   1. maximal and durable suppression of viral load to reduce the risk of disease progression
   2. restoration and/or preservation of immunologic function
   3. improvement in quality of life
   4. reduction in HIV-related morbidity and mortality
   5. prevent transmission of HIV

C. laboratory parameters for HIV
   1. virologic suppression can be defined as a sustained reductiojn in HIV RNA level below the assay limit of detection (<50 copies/ml)
   2. viral load assessment predicts:
      i. course of disease ii. need for ARV iii. which ARV to utlize
      iv. clinical response to ARV
   3. viral *load testing* is different from *resistance testing*

D. When to begin ARV
   1. The decision to begin ARV is based on an assessment of disease progression risk.
   2. Indicators for initiation of ARV include:
      i. a history of AIDS-defining illness
      ii. CD4 count <500 cells/mm^3 iii. Pregnancy
      iv. HIV-associated neuropathy
      v. HBV co-infection when HBV treatment is indicated
   3. Check for latest ARV guideline updates on **AIDSinfo.nih.gov.**

4. Starting ARV if CD4>500 cells/ul has both "pros" (may reduce morbidity and transmission) and "cons" (toxicity, resistance and cost)

II. FDA approved drugs available for treatment of HIV infection- 6 major drug classes



HIV-2 infection

1. Endemic to west Africa, should be considered in that population or if patient has contact with that population
2. Generally shows longer asymptomatic stage, lower viral loads and mortality
3. Multispot HIV-1/HIV-2 Rapid test is approved for differentiating HIV-1 from HIV-2, but most serology and viral load tests are unreliable for HIV-2
4. HIV-2 should be considered in patients when serology and/or viral load are negative but CD4 and clinical conditions suggest HIV infection
5. NNRTI **not** effective against HIV-2. Use clinical improvement and CD4 count improvement to assess response to treatment.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)

1. **General mechanism of action-**nucleoside or nucleotide analogs that lack 3' hydroxyl group enter the cells, are phosphorylated and form sythetic

substrates for viral RT. NRTI compete with native nucleotides, and terminate proviral DNA when incorporated

2. **Onset and duration-** NRTIs generally eliminated from plasma by renal excretion with half-lifes of 1-10 hours, intracellular reservoirs more persistent. One or two doses daily except zalcitabine (every 8h). Only didanosine has food restrictions.
3. **Relative effectiveness at reducing viral load-** Modestly effective as monotherapy (not recommended), valuable when used in combination therapy. Resistance develops slowly compared to NNRTIs or PIs.
4. **Major adverse effects-** Some in this class capable of inhibiting mitochondrial DNA polymerase, toxicities include anemia, myopathy, and pancreatitis and are associated with serious **lactic acidosis-hepatic steatosis syndrome.** (**didanosine > stavudine > zidovudine**) ***
5. **HBV flare** is the increase in HBV titer when NRTI that have anti-HBV activity are discontinued (emtricitabine, lamivudine and tenofovir)
6. **Class members currently in use:**
   a. **Abacavir**
      i. **Indication**: activity against HIV-1
      ii. **Adverse effect**: associated with serious hypersensitivity reaction in patients with HLA-B 5701 genotype
      iii. **Contraindicated**: in patients with HLA-B 5701 genotype***
   b. **Zidovudine (AZT)**
      i. **Indications:** activity against HIV-1 and HIV-2, used as exposure prophylaxis, OK for children or adults and in pregnancy
      ii. **Major adverse effects:** anemia and neutropenia iii. **Contraindications:** do not co-administer with stavudine (antagonist)
      iv. **Significant drug interactions:** cotrimoxazole or ganciclovir (bone marrow toxicity), ribavirin (antagonist)

B. *Nonnucleotide reverse transcriptase inhibitors (NNRTI)*

1. **General mechanism of action-** noncompetitive inhibitors that bind to reverse transcriptase and induce a corformational change that greatly reduces enzyme activity
2. **Onset and duration-** rapidly absorbed and metabolized by hepatic CYPs, half-lives range from delavirdine (2-11h) to efavirenz (40-50h)
3. **relative effectiveness at reducing viral load-** Activity against HIV-1 but not HIV-2. Resistance can develop rapidly, never use a monotherapy. One **advantage** of NNRTI-based regimen is that PIs can be reserved for later and thus avoid PI adverse effects. The **disadvantages** are the prevalence of resistant virus, low genetic barrier to resistance.

4. **Major adverse effects/drug interactions:** all influence CYP activity, so drug interactions common.

Cytochrome P450 system and HIV drug metabolism

- the P450 cytochromes influence drug metabolism by oxidizing or reducing substrate drugs
- P40 substrate drug metabolism is dependent on one or more P450 enzymes (e.g. CYP3A4)
- a P450 inhibitor is a drug that inhibits the metabolism of a P450 substrate
- a P450 inducer stimulates increased expression of P450 enzymes, increases substrate metabolism

5. **FDA-approved class members currently in use:**
   a. **Efavirenz**
      i. **Indications:** preferred as part of initial antiretroviral therapy, the only once daily dose NNRTI
      ii. **Major adverse effects:** birth defects, transient CNS effects
      iii. **Contraindications:** 1st trimester pregnancy or women planning to conceive***
      iv. **Significant drug interactions:** CYP3A4 inducer, so reduces concentration of PIs, methadone
   b. **Nevirapine**
      i. **Indications:** recommended as an alternative to Efavirenz in treatment naïve women with pretreatment CD4<250 cells/mm and men with CD4<400 cells/mm
      ii. **Major adverse effects:** severe hepatotoxicity iii. **Contraindications:** women with pretreatment CD4 >250 cells/mm^3 and men with pretreatment CD4 >400 cells/mm^3 ***
      iv. **Significant drug interactions:** CYP inducer, reduces concentration of methadone, PIs

C. Protease inhibitors (PI)

1. **General mechanism of action-** specifically and reversibly inhibit the HIV aspartyl protease and thereby block post-translational processing of viral proteins required to produce a mature viral particle
2. **Onset and duration-** Most PIs have poor bioavailability, absorption of some enhanced by high fat meals, all metabolized by hepatic CYP system
3. **Relative effectiveness at reducing viral load:** highly effective as part of combination therapy

4. **Major adverse effects:** associated with metabolic syndrome, lipodystrophy, lipoatrophy of face and limbs, lipemia, nausea, vomiting, diarrhea and paresthesias. All are substrates and inhibitors of CYPs.
5. **Class members currently in use:**
   a. **Ritonavir**
      i. **Indications:** active against HIV-1 and 2, **potent CYP3A4 inhibitor** that is used to boost availability of drugs that are CYP3A4 substrates and to reduce dose and dosing frequency
      ii. **Major adverse effects:** not well tolerated at doses required for antiviral activity, but low doses used for boosting are well tolerated, paresthesias
      iii. **Contraindications/significant drug interactions:** similar to other PIs
6. **Ritonavir (RTV) "boosting" of PIs*****
   a. ritonavir is a PI that is a potent CYP3A4 inhibitor
   b. co-administration of low dose ritonavir enhances or "boosts" exposure of other PIs
   c. RTV boosting allows for reduced dose and dosing frequency
   d. low dose RTV improves tolerance and is effective at CYP3A4 inhibition
      i.

PI-induced metabolic syndrome

Definition: a cluster of metabolic risk factors that tend to occur together that increases chances of developing heart disease, stroke, and/or diabetes and are associated with PI therapy

-hyperlipidemia, hypertriglyceridemia, decreased HDL and increased LDL

-insulin resistance, hyperinsulinemia

-lipodystrophy, central obesity, facial and limb lipoatrophy

-increased macrophage CD36 leading to increased cholesterol uptake, atherosclerosis

ARV and management of dyslipidemia/statin usage

- prior to treating cholesterolemia in HIV-infected patients undergoing ARV, consider statin metabolism
- should avoid combining CYP3A4 substrate statins with boosted PIs
- switching from PIs to NRTIs may alleviate lipodystrophy, hyperlipidemia

Statins as CYP3A4 substrates

Yes	No
simvastatin	pravastatin
atorvastatin	fluvastatin
lovastatin	

D. ***Viral integrase inhibitors***- **Raltegravir**

1. **Mechanism of action:** blocks insertion of reverse-transcribed viral DNA into the host DNA
2. **Indications:** in combination therapy for experienced patients with suppression failure or excess toxicity
3. **Onset and duration:** twice daily dose following high fat meal
4. **Relative effectiveness at reducing viral load:** effective when combined with PI and NRTI
5. **Major adverse effects:** diarrhea, headache, and nausea
6. **Contraindications:** not for use as monotherapy

E. ***Fusion inhibitors***- **Enfuvirtide**

1. **General mechanism of action:** peptide inhibitor that binds HIV surface glycoprotein gp41 to block conformation required for membrane fusion with host cell
2. **Indications:** combination therapy component in experienced patients with viral suppression failure. **Injected** twice daily
3. **Relative effectiveness at reducing viral load:** not active against HIV-2, mutation of the HR1 region of gp41 associated with resistance
4. **Major adverse effects:** Injection site reaction/inflammation is very common, hypersensitivity
5. **Contraindications:** do not use in patients with known hypersensitivity

F. ***CCR5 antagonists*- Maraviroc**

1. **General mechanism of action:** small molecule slowly-reversible antagonist of the CCR5 interaction with gp120, blocks CCR5-tropic HIV-1 entry
2. **Indications:** combination therapy component for experienced patients with viral suppression failure, should perform **tropism test** first
3. **Resistance mechanisms:** mutation of the CCR5-binding amino acid sequence in HIV gp120, or emergence of CXCR4-tropic virus
4. **Major adverse effects:** hepatotoxicity and possible hypersensitivity
5. **Contraindications:** liver dysfunction
6. **Significant drug interactions:** CYP substrate, concentration altered by CYP inducers and inhibitors

III. Combination therapy for HIV infection

A. Complicating conditions and considerations:

1. comorbid conditions such as cardiovascular disease, chemical dependency, **tuburculosis**, renal, liver, or psychiatric disease
2. potential adverse drug effects
3. potential drug interactions with other medications
4. pregnancy
5. results of drug resistance testing
6. HLA-B5701 testing if considering Abacavir
7. gender and pretreatment CD4 count if considering Nevirapine
8. likelihood of patient adherence with the regimen

B. Tuberculosis treatment for HIV-infected patients

1. Rifampin-based antimycobacterials are highly effective in treating MTB infection. Rifamycin is a potent inducer of CYP activity, and markedly effects exposure to multiple ARV drugs.
2. Rifampin dramatically reduces exposure to all PIs and multiple NNRTIs and should not be coadministered (except efavirenz).***
3. Rifabutin is preferred drug for HIV patients with active MTB, but still interacts with PIs and requires caution.
4. Bottom line is that coadministration of rifabutin and ARV will require monitoring and dose adjustment.

C. Initial ART regimens: DHHS categories

1. Preferred- trials show optimal efficacy, durability, tolerability and toxicity profiles
2. Alternative- effective but have disadvantages
3. Acceptable- less virologic efficacy, or greater toxicities
4. May be acceptable but should be used with caution- effective in some studies, but has safety, resistance, or efficacy concerns.

D. Combination ARV options for treatment-naïve patients-recommended starting regimen consists of either **1 NNRTI + 2 NRTI**, or **1 PI (preferably boosted with ritonovir) + 2 NRTI.*****

NNRTI options:

Recommended	Efavirenz	**Do not use** in 1st trimester of pregnancy or patients with high pregnancy potential
Alternate	Nevirapine	**Do not use** in patients with moderate to severe hepatic impairment, or in women with pre-ART CD4>250 mm^3 or men with pre-ART CD4>400 mm^3

PI options:

preferred	Atazanavir + ritonavir	Do not use in patients who require high dose proton pump inhibitors
preferred	Darunavir + ritonavir	
preferred	Fosamprenavir + Ritonavir (twice daily)	
preferred	Lopinavir + ritonavir	Do not use in pregnant women
alternative	Unboosted atazanavir	Do not use in combination with tenofovir or didanosine/lamivudine
alternative	Fosamprenavir + RTV (once daily) or unboosted	
alternative	Saquinavir + ritonavir	

Dual-NRTI options

preferred	Tenofovir + emtricitabine	Do not use with unboosted atazanavir. Use with caution with nevirapine or in patients with underlying renal insufficiency
alternative	Abacavir + lamivudine	Do not use when positive for HLA-B 5701. Caution: HIV RNA>100,000 copies/ml or in high risk of cardiovascular disease.
	Didanosine + lamivudine (or emtricitabine)	Do not use with unboosted atazanavir or in patients with history of pancreatitis or peripheral neuropathy.
	Zidovudine + lamivudine	Use with caution in presence of pretreatment anemia and/or neutropenia

E. Changing drug regimen due to treatment failure (virologic or immune)
   1. **Definition of virologic suppression failure:** the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL) and may manifest as:
      a. incomplete virologic response to therapy, or
      b. virologic rebound (after virologic suppression, repeated detection of HIV RNA above the assay limit of detection)
   2. **Definition of immune failure:** the inability to achieve and maintain adequate CD4 T-cell response despite virologic suppression
   3. Assess drug resistance- drug resistance test, prior treatment history, prior resistance results.
   4. Clarify goals to re-establish maximum virologic suppression
   5. Evaluate remaining ARV options
   6. Base ARV selection on medication history, resistance testing
   7. Avoid treatment interruption

F. What **NOT** to use

Regimens	**rationale**	**exception**
Monotherapy with NRTI	1. Rapid resistance development. 2. Inferior antiretroviral activity	none
Dual NRTI regimens	1. Rapid resistance development. 2. Inferior antiretroviral activity	none
Triple NRTI regimens	High rate ofnonresponse in treatment-naïve patients	Abacavir/zidovudine/ Lamivudine or tenofovir/ Zidovudine/lamivudine in patients for whom other options are worse.

What **NOT** to use (continued)

Components	**rationale**	**exception**

Atazanavir + indinavir	Potential hyperbilirubinemia	none
Didanosine + stavudine	High incidence of toxicity, potential serious lactic acidosis	When other options not available
Double NNRTI combo.	EFV + NVP has more adverse effects than separate, both reduce ETV	none
EFV in 1st trimester	teratogenic	When other options not available
Emtricitabine + lamivudine	Similar resistance profile	none
Etravirine + unboosted PI	Induced PI metabolism	none
Etravirine + boosted ATV, FPV, or TPV	Induced PI metabolism	none
Nevirapine in naïve women with CD4>250, men CD4>400	High incidence hepatotoxicity	When other options not available
Stavudine and zidovudine	antagonistic	none
Unboosted darunavir, saquinavir, or tipranavir	Inadequate bioavailability	none

Study focus areas:

1. ARV drug mechanism of action
2. Severe adverse effects
3. Contraindications
4. Major drug interactions
5. Recommended combination therapy for treatment of naïve patients
6. Combination therapy regimens NOT recommended
7. Summary tables

Example of a test question:

A 29 year-old male was previously diagnosed with M. tuberculosis infection and rifampin treatment was initiated. In a follow up exam, lab results reveal the patient to be infected with HIV, and lab results are as follows: CD4+ count = 460 cells/mm^3

viral load = 41,000 copies/ml

resistance testing = HIV1

Which of the following treatment regimens would be a recommended option, if any?

A. efavirenz, tenofovir, and emtricitabine
B. Nevirapine, tenofovir, and emtricitabine

C. Atazanavir, abacavir, and lamivudine
D. Didanosine, abacavir, and lamivudine
E. None of the above

Summary tables:

NRTI summary table

Agent	Preferred for naïve patients	Adverse effects	Contra-indications	Drug interactions
Abacavir		hypersensitivity	HLA-B 5701+	
Didanosine		peripheral neuropathy	Stavudine, zalcitabine	tenofovir
Emtracitabine	yes	HBV flare	lamivudine resistance	
Lamivudine		HBV flare	emtracitabine resistance	zalcitabine
Stavudine		lactic acidosis, lipid metabolism	Zidovudine res., ddI co-admin.	zidovudine
Tenofovir	yes	HBV flare, renal toxicity	ddI/EFV Co-admin.	↑didanosine, ↓atazanavir
Zidovudine		anemia and neutorpenia	coadministering stavudine	Cotrimoxazole or ganciclovir, ribavirin

Examples of drugs that should NOT be coadministered PIs due to CYP-dependent metabolism

Drug	CYP3A4 role	Class
Quinidine	substrate	antiarrhythmic
Ergotamine	substrate	Ergot derivative
Rifampin	strong inducer	antimycobacterial
Midazolam	substrate	benzodiazepine
Phenobarbitol	strong inducer	barbiturate
Warfarin	substrate	anticoagulant
St. John's Wart	strong inducer	herbal

NNRTI summary table

Agent	Preferred for naïve patients	Adverse effects	Contra-indications	Drug interactions
Delavirdine		Rash	Naïve patients	PIs, phenytoin, phenobarbitol, carbamazepine
Efavirenz	Yes	Birth defects, transient CNS	1st trimester pregnancy	PIs, methadone
Etravirine		Rash	coadministering with other NNRTIs or some PIs	PIs, other CYP substrates
Nevirapine		Severe hepatotoxicty	female CD4>250 male CD4>400	Methadone, some PIs
Rilpivirine		?	?	PIs

PI summary table

Agent	Preferred for naïve patients	Adverse effects	Contra-indications	Drug interactions
atazanavir	yes	bilirubinemia	Hepatic insuff.	See list
fosamprenavir	yes	rash	Sulfa allergy	" (and glucuronidation inh)
indinavir		Kidney stones, bilurubinemia, IR	Rifampin co-administration	"
lopinavir	yes	Lipemia, GI, lipodystrophy	Rifampin co-administration	"
nelfinavir		diarrhea	"	"
ritonavir		paresthesias	"	"
saquinavir		lipodystrophy rash, anemia	Co-administration with rifampins, efavirenz, nevirapine	"
darunavir	yes	rash	Sulfa allergy	"
tipranavir		Hepatitis, ↑lipids,glucose	Sulfa allergy	"

Pharmacology and Therapeutics

Anti-Viral Drugs

April 24, 2014

Thomas Gallagher, Ph.D.

LEARNING OBJECTIVES:

1. Describe the stages of antiviral drug discovery and development.
2. Discuss the clinical practices contributing viral drug resistance.
3. Name the drugs blocking influenza virus and HIV entry and describe their mechanisms of action.
4. Categorize the drugs blocking virus replication into "nucleoside" and "nonnucleoside" based inhibitors; compare and contrast how members of each group arrest virus replication.
5. Compare the antiviral mechanisms of acyclovir and azidothymidine, emphasizing their similarities and differences.
6. Distinguish between neuraminidase inhibitors (blocking flu) and protease inhibitors (blocking HIV) with respect to the mechanisms by which each prevents virus spread.
7. Discuss how combination drug therapies help to prevent the development of virus resistance to antiviral drugs.

KEY CONCEPTS:

1. Challenging pipeline to antiviral drug approvals
2. Facile generation of drug-resistant mutants; resistant mutants pre-exist and are abundant

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3. Antiviral drug targets thwart virus only (not cell) and thus turn out to be unique to particular virus
4. Most antiviral drugs arrest at the virus replication stage

5. Long-term antiviral administration is needed to combat persistent viruses, notably HIV
6. Combination antiviral drug therapy limits the expansion of drug-resistant viruses

LECTURE OUTLINE – ANTIVIRAL DRUGS

1. The need for antiviral drugs
2. Explanation for the limited antiviral drug arsenal

3. Drugs blocking virus entry
4. Drugs blocking virus replication
5. Drugs blocking virus morphogenesis or dissemination

6. The problem of antiviral drug resistance
7. The benefits of combination drug therapy

SPECIFIC POINTS:

1. The need for antiviral drugs

Note that most viral diseases are mild and self-limiting, and probably do not require specific antiviral therapies. Most of the clinician's antiviral drugs are for serious infections, notably HERPES VIRUSES, HEPATITIS VIRUSES, INFLUENZA AND PARAMYXOVIRUSES, and HIV. For some of these

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viruses, vaccines are unavailable, so antiviral drugs are the current treatment.

2. Explanation for the limited antiviral drug arsenal

Virus "biology" is linked to cell biology, so most antiviral drugs are cytotoxic. Only a few have therapeutic windows sufficient for clinical use. The road from laboratory antiviral to clinical drug is long and expensive, and the time period for clinical drug utility is short (short prescription time periods and loss of drug utility due to virus adapting drug resistance). Therefore, few antivirals are developed for clinical use.

3. Drugs blocking virus entry

Most clinical antivirals block at the replication stage, but there are a few recently developed drugs that indicate entry blockade as a tenable antiviral approach.

Pleconoril, (blocks nonenveloped picornavirus entry) is used for compassionate use in otherwise lethal cocksackie virus infections. The drug was rejected by FDA because of side effects, headache, nausea, diarrhea.

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Abreva, OTC topical herpes antiviral, blocks HSV entry and speeds resolution of cold sores. No overt side effects noted.

Miraviroc (blocks CCR5, thus anti-HIV entry) is FDA approved, has high safety profile. There are other CCR5 receptor antagonists, Cenicriviroc, Vicriviroc, that also block HIV. Note that HIV can use uther cytokine receptors for entry, i.e., CXCR4, so these drugs cannot block all HIV entry.

Enfuvirtide (Fuzeon) is an HIV fusion inhibitor, blocks HIV entry. This is a peptide drug, very expensive ($25K /year),really only used as last stage salvage therapy. Must be injected, has many side effects,including injection site reactions and immune hypersensitivity reactions.

Amantadine and rimantadine block influenza A viruses. There may be a USMLE question about amantadine and its blockade of IAV, blocks viral M2 and prevents dissociation of viral RNAs from virus M1 proteins. These drugs have CNS side effects. Notably, their overuse has made them obsolete, as most IAV is amantadine resistant, hence they are no longer widely recommended for flu disease.

4. Drugs blocking virus replication

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Most of these drugs are nucleoside analogs. Note the importance of the 3’ –OH in dNTPs and NTPs, and the absence of the 3’ –OH in many antivirals.

Acyclovir is a widely used anti-HSV drug. Viral kinases phosphorylate this drug, and viral DNA pol has high specificity for acyclovir triphosphate. The drug acts as a chain terminator. The drug does not block mutant viruses lacking kinase activity or mutants in viral DNA pol. The drug is also prescribed for chicken pox and shingles (VZV), but only partially inhibits CMV. Acyclovir has a high safety profile but can cause neurologic side effects. Acyclovir is poorly bioavailable hence the pro-drug valyl form is often used, especially for oral administration. USMLE step 1 tests sometimes include questions about acyclovir.

AZT (Zidovudine) is a first stage anti HIV drug, a classic chain terminator. Specificity comes at the level of the viral RT. Notably AZT is not used alone but as a component of HAART. AZT is also used in combination with lamivudine in postexposure prophylaxis. Side effects of AZT are anemia, neutropenia, hepatotoxicity, cardiomyopathy, myopathy. Resistance is with viral RT mutations.

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Lamuvidine is another chain terminator. Blocks HBV and also HIV. Synergistic with AZT.

Ribavirin is used mostly for HCV, the standard regimen for chronic HCV being ribavirin plus pegylated type I interferon. Ribavirin is a nucleoside analog but is not a chain terminating agent. MOA is not entirely clear. A principal side effect is mutagenicity. Ribavirin is a known teratogen and should not be given in pregnancy. Ribavirin has also been used to block many zoonotic viral infections, including SARS, viral hemorrhagic fevers, and also in pediatric respiratory syncytial virus infections.

Foscarnet is an interesting non-nucleoside replication inhibitor, a mimic of the pyrophosphate leaving group. This drug is prescribed for acyclovir-resistant herpes infections and is approved for CMV diseases. Nephrotoxicity is the most common adverse effect of this drug.; can also cause anemia.

Herpes helicase inhibitors are nearing FDA approval, and will likely supplant foscarnet as the drug of choice in cases where acyclovir and its derivatives are unable to control HSV, VZV .

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HCV protease inhibitors (Telaprevir and Boceprivir) block an intracellular, virus encoded HCV protease and therefore prevent the proteolytic processing of the HCV polyprotein. The effect is a block in virus replication. These drugs have just come into clinical use, but their effectiveness appears to be remarkable. In conjunction with ribavirin and interferon, these HCV specific protease inhibitors can essentially "cure" patients of HCV, at least the genotype 1a form (there are several HCV genotypes that are resistant to the current protease inhibitors).

5. Drugs blocking virus morphogenesis or dissemination

HIV protease inhibitors (many names) block the HIV protease and thus prevent virion morphogenesis. They are a standard part of HAART. MOA is as a enzyme transition state analog. The drugs are peptidomimetics and block the protease active site. The side effects include altered adipocyte metabolism, causing lipodystrophy, and also kidney stones (the drugs are insoluble).

Neuraminidase inhibitors (Tamiflu and Relenza) are influenza inhibitors, now widely used because amantadine is ineffective. The drugs block release of viruses from infected cells, limiting virus dissemination in the lung. They reduce infection by a day or two, and in severe IAV infections, limit

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the likelihood of acute respiratory distress. Side effects are rare and include headache, nausea, vomiting. There is some concern that the drugs elicit neuropsychiatric effects (hallucinations, etc).

6. The problem of antiviral drug resistance

Note error frequencies in RNA virus infections are high, 10-exp4, and therefore drug resistance is a certainty. One can easily estimate the frequencies of pre-existing drug resistant mutants in a virus population, assuming that one mutation can confer drug resistance. These estimates help clarify how readily drugs, such as IAV neuraminidase inhibitors, can select for uniformly drug-resistant virus populations.

7. The benefits of combination drug therapy

One solution to the problem of antiviral resistance is to employ combination therapies, such as HAART for HIV infections.

Dietary Supplements and Herbal Medications

Learning Objectives

(i) Define Dietary Supplements and Herbal Medications

(ii) List the claims manufacturers can make regarding Dietary Supplements and Herbal Medications

(iii) Define the role of the Federal Drug Administration (FDA) in the regulation of Dietary Supplements and Herbal Medications

(iv) List the reasons why it is important to ask patients about their consumption of Dietary Supplements and Herbal Medications

(v) Identify those patient populations that can benefit from taking vitamins and other dietary supplements

(vi) List the major toxicities associated with overdose of vitamins and other dietary supplements

(vii) Identify the most common uses for the most popular herbal medications

(viii) Identify the major adverse effects of the most popular herbal medications

(ix) Identify any major drug interactions associated with the use of the most popular herbal medications

Supplements to be covered:

Vitamin A
Vitamin B6, B12
Vitamin C
Vitamin D
Vitamin E
Vitamin K

Calcium
Chromium
Iodine
Iron
Magnesium
Selenium
Zinc

Herbal medications to be covered:

Aloe Vera
Bitter Orange Black Cohosh
Cranberry
Echinacea
Ephedra
Feverfew
Garlic Ginger
Gingko
Gingseng
Hawthorn
Horse Chestnut
Kava
Milk Thistle
Saw Palmetto
St. John's Wort
Valerian
Yohimbe