Cancer

Chemotherapy

Women are more likely to die of colon cancer than men and yet the cause is unknown. Is it a difference in treatment? READ the abstract from a paper about gender differences in colon cancer.

Cancer starts with a cell that is genetically different from the surrounding cells

All cell types can become cancerous and there are many causes of cancer. The difference between a noncancerous cell and one that has gone rogue may be explained as the loss of an internal braking mechanism on growth.

The National Cancer Institute at the National Institutes of Health has an A-Z list of Cancers.
**Antiemetics… see GI lecture**

- **Aprepitant** *(Emend)*
- **Dexamethasone** *(Dexasone)*
- **Diphenhydramine** *(Benadryl)*
- **Dronabinol** *(Marinol)*
- **Haloperidol (Haldol), Droperidol** *(Inapsine)*
- **Metoclopramide** *(Reglan)*
- **Ondansetron** *(Zofran)*
- **Prochlorperazine** *(Compazine)*
- **Scopolamine** *(Scopace, Transderm Scop)*

Irritant antineoplastics trigger 5-HT release from enterochromaffin cells in the GIT which leads to hypermotility of the GIT: vomiting, nausea, diarrhea.

Excess 5-HT is absorbed into blood where platelets soak up as much as possible. Excess 5-HT circulates to brain to stimulate receptors on CTZ triggering vomiting.

**Mechanisms of Resistance to Chemotherapy**

**INNATE**
Tumor possesses resistance before therapy:
- Pumps
- Enzymes

**ACQUIRED**
Changes in the tumor as a result of treatment:
- Gene mutations
- Altered gene expression

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**Hematopoietic agents**

Colony stimulating factors are chemicals that promote the differentiation of stem cells into particular cell types. In cancer chemotherapy, there tends to be a lot of bone marrow suppression, leading to deficiencies of blood cells.

WBC Growth Factors help replenish neutrophils.

1. **Filgrastim** *(Neupogen)* – granulocyte colony-stimulating factor (biologic)
2. **Pegfilgrastim** *(Neulasta)* – filgrastim bound to a protein to slow metabolism
3. **Sargramostim** *(Leukine)* – granulocyte-macrophage colony-stimulating factor

RBC growth factors mimic erythropoietin, and are associated with increased mortality.

1. **Epoetin alfa** *(Procrit)* – recombinant erythropoietin
2. **Darbepoetin alfa** *(Aranesp)* – synthetic erythropoietin
Alkylation Agents

The Nitrogen Mustards are a large and important group of antineoplastic drugs. During WWI, German chemists developed sulphur and nitrogen mustards as war gases. It was widely recognized at the time that exposure to these gases caused leukopenia (and was often fatal).

In the early 1940’s Doctors Louis Goodman and Alfred Gilman realized alkylation agents could be developed as chemotherapeutic agents. The two pharmacologists were recruited by the US Department of Defense to investigate the war gases for other potential applications. Goodman and Gilman went on to author an authoritative textbook on Pharmacology. I, myself, have four editions of this amazing text.

The nitrogen mustards are one type of alkylation agent. Alkylation is a chemical reaction in which an alky group (a series of single-bonded carbon and hydrogen atoms, like a methyl or ethyl group) is attached to another molecule, in this case either proteins or nucleic acids. Most of the alkylation agents used to treat cancer alkylate DNA, a reaction that leads to the cross-linking of the DNA chains. The strands are then unable to uncoil, separate and replicate, so the affected cells die.

The true alkylation agents used in cancer therapy include the nitrogen mustards, the nitrosoureas and the alkyl sulfonates. Included in our lecture notes is Cisplatin (Platinol) a Platinum-based drug with an alkylation-like mechanism using platinum instead of an alkyl group. A benefit of using the platinum is it acts to focus radiation on the tumor if radiation therapy is used in conjunction with the chemotherapy.

Chlorambucil (Leukeran) and Cyclophosphamide (Cytoxan) are two classic nitrogen mustard alkylation agents. These agents are used primarily in WBC cancers (lymphomas, leukemia and myelomas). Chlorambucil is not curative, but may provide palliation. Cyclophosphamide is also used to treat breast, ovarian, small cell lung cancers, neuroblastoma and retinoblastoma, sarcomas, nephrotic syndrome, and as an immunosuppressant for organ or bone marrow transplants. Both drugs are strongly myelosuppressive and may cause secondary malignancies. They are associated with significant toxicity.

Carmustine (BCNU or BiCNU) is a nitrosourea alkylation agent. Again, these agents cause DNA to crosslink preventing the uncoiling, separation and replication of DNA. Carmustine is palliative, but otherwise similar to cyclophosphamide. It is used in cocktails to treat many of the same cancers. It, too, is extremely toxic causing bone marrow suppression and pulmonary fibrosis among other things.
Cisplatin was first discovered in 1845, but not recognized as cytotoxic until the 1960’s and not registered as a new molecular entity with the FDA until 1978. Cisplatin is not technically an alkylating agent, because it does not crosslink DNA by inserting an alkyl group, it uses platinum. Platinol is used in combination therapy to treat testicular, ovarian and bladder cancers. There is a pharmacogenomic consideration with Cisplatin. Children with a particular genetic variant for a Phase 2 enzyme (thiopurine S-methyltransferase) are at an increased risk of ototoxicity. About 11% Caucasians and African Americans express this variant and are at risk.

Methotrexate (Trexall, Rhematrex) is an antimetabolite used to treat certain cancers, severe psoriasis and adult rheumatoid arthritis. Like the antibiotic Trimethoprim, Methotrexate inhibits the enzyme dihydrofolic acid reductase. Therefore, methotrexate interferes with DNA synthesis and repair, and ultimately, cell replication. This drug has an astonishingly long list of boxed warnings and severe side effects. The risk of serious toxicity is very high. Folinic acid (Leucovorin) is indicated to diminish the toxicity and counteract the effects of overdoses of methotrexate. Methotrexate and Leucovorin are on the FDA drug shortages list.

Flurouracil (5-FU, Adrucl, Carac) is an antimetabolite that also interferes with the synthesis of DNA but via another pathway. It is palliative for the management of carcinomas of the colon, rectum, breast, stomach and pancreas. It too has a long list of serious side effects, but not as many or as bad as methotrexate.

Asparaginase (Elspar) is an enzyme, a natural product used as part of a chemo-cocktail to treat acute lymphoblastic leukemia (ALL). It is synthesized using recombinant technology in E. coli. Serious allergic reactions, thrombosis and coagulopathy, pancreatitis, glucose intolerance, and liver toxicity are concerns with Asparaginase.

Tumor Lysis Syndrome

Remember, long ago, and far away, back in the Pain and Inflammation lecture on NSAIDs, we covered drugs used to treat Gout?

Two of those drugs, Allopurinol (Zyloprim) and Rasburicase (Elitek) are indicated to treat hyperuricemia secondary to cancer chemotherapy.

The question remains, why does chemotherapy cause gout?
The answer: Tumor Lysis Syndrome.

As the drug kills cells, a flood of cell contents, and the break-down products of those contents, enters the blood, causing:
- Hyperkalemia
- Hyperphosphatemia
- Hyperuricemia
- Hypocalcemia (which leads to tetany)
- Acute renal failure

Guidelines for treatment of TLS
Vincristine (Oncovin) is an alkaloid from a common flowering herb, the Madagascar periwinkle (Vinca rosea). It is a natural product originally known as leurocristine. Vincristine inhibits the formation of mitotic spindles by blocking the assembly (polymerization) of microtubules in cells readying for division. It is mainly used to treat leukemia, but is used in chemo-cocktails to treat a variety of other cancers.

Etoposide (Eposin) is a semisynthetic derivative of podophyllotoxin from the mandrake plant. It is called a natural product and is a topoisomerase inhibitor. This is an enzyme that repairs breaks in the DNA strands. Without the enzyme, breaks cannot be repaired.

Doxorubicin (Adriamycin) is an anthracycline antibiotic, another natural product, this time produced by fungi. Doxorubicin appears to act by intercalation. This is where a chemical inserts itself into the DNA (or RNA or protein) chain and interrupts its ability to function. Doxorubicin binds to DNA and RNA polymerases and with the cell membrane. Doxorubicin has a maximum cumulative, life time dose of 550 mg/m². It is cardiotoxic. After 300 mg/m² (55% of maximum dose), Dexrazoxane (Cardioxane) is given to provide some cardioprotection.

Doxorubicin is considered to be the most important antineoplastic drug by many oncologists. It comes in two forms. The liposomal formulation is a product that encapsulates the doxorubicin in a lipid membrane, improving distribution to the tumor. Both forms are on the FDA shortages list.

Bleomycin (Blenoxane) is also an antibiotic, actually a mixture of antibiotics. It is used in the palliative treatment of squamous cell carcinomas, testicular cancer and lymphomas. It is also used as a sclerosing agent for malignant pleural effusion. Sclerosing agents are tissue irritants that cause vascular thrombosis and endothelial damage that leads to the obliteration of a blood vessel when the material is injected into or adjacent to blood vessels.

Tamoxifen (Nolvadex, Soltamox) is derived from the Pacific yew tree. It is a nonsteroidal antiestrogen. It is used in estrogen receptor positive metastatic breast cancer, ductal carcinoma in situ and to reduce breast cancer incidence in high-risk women. It is associated with an increased incidence of uterine malignancies.

Leuprolide (Lupron) is the super gonadotropin releasing hormone (GnRH) agonist covered in the Endocrine lecture. The depot form of Lupron is indicated for palliative treatment of advanced prostatic cancer. Leuprolide is also used to treat endometriosis, breast cancer, uterine leiomyomata, precocious puberty and as a fertility drug in women having difficulty conceiving. Leuprolide acts acutely to increase secretion of FSH and LH, but when given chronically, it shuts down the synthesis and secretion of these hormones.

Tamoxifen and Leuprolide have very similar types of adverse reactions. They are both hormone modulators that can cause hot flashes, weight gain, thromboembolism and nausea and vomiting.
Cancer chemotherapy is not necessarily curative

Cancer is the 2nd leading cause of death in the US, following cardiovascular death. The effectiveness of chemotherapy differs dramatically based on a number of variables, most important of which is which type of cancer someone has.

Cancers for which therapy is OFTEN CURATIVE:
- ALL, Hodgkin’s, diffuse histiocytic lymphomas, Burkitt’s lymphoma, testicular cancer and choriocarcinomas.

Cancers for which therapy is PROBABLY CURATIVE:
- AML, small cell lung cancer, breast cancer, osteogenic sarcomas

Cancers for which therapy has MAJOR BENEFITS:
- Head & neck cancers, cervical cancer, metastatic breast cancer, ovarian cancer, soft tissue sarcomas, nodular lymphomas, chronic leukemia, insulinomas

Cancers for which therapy has LIMITED EFFECTIVENESS:
- Lung, GI, prostate, melanoma

Homework and Exercises

1. **Read the “START HERE” announcement in Laulima for updates and instructions.**
2. Read about the Cancer in Chapters 59 & 60 of Adams & Urban, PHARMACOLOGY Connections to Nursing Practice.
3. Review the Powerpoints and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for this lecture. Review any handouts available for this lecture in the Course Index.
4. Complete the SLO practice set for Cancer in Tasks, Tests and Surveys.
5. Use “Chat,” “Discussions and Private Messages” or the lecture “Forum” to ask questions and find answers or to seek assistance.
6. Complete the online quiz in Laulima, Tasks, Tests and Surveys.

If you have any questions, email me at gbeale@hawaii.edu