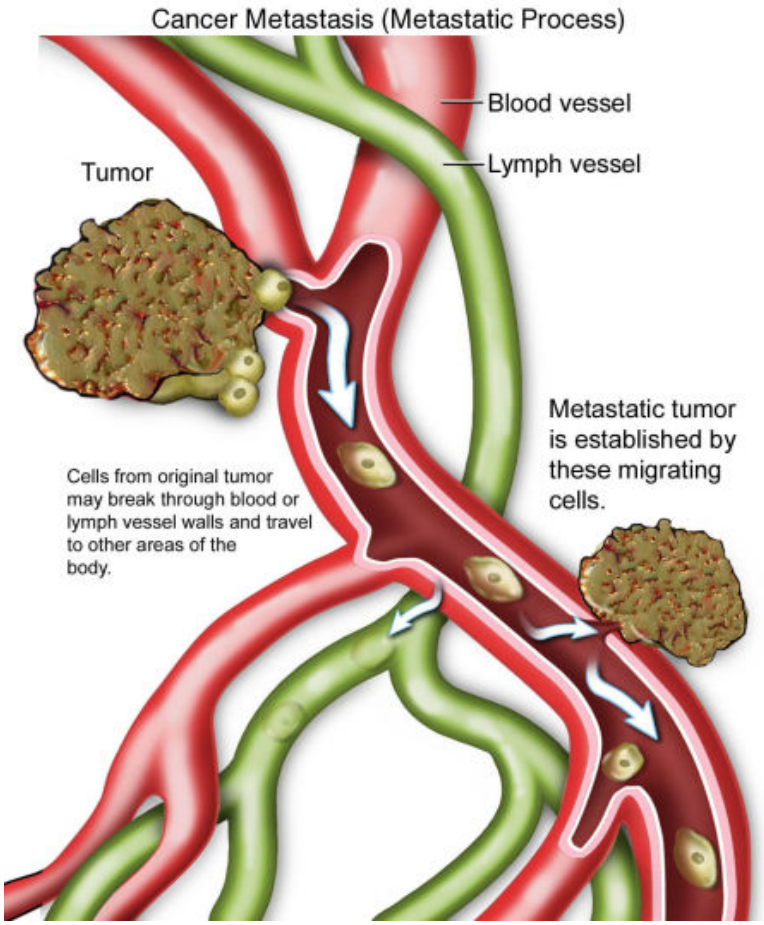
Module 17 – Cancer Chemotherapy

17.1 – Cancer

Cancer – refers to the uncontrolled proliferation of cells. Cancer cells are often referred to as neoplastic, meaning they have abnormal and uncontrollable cell growth.

<u>Characteristics of Cancer Cells</u>

1) Persistent uncontrollable cell proliferation
2) Invasive – cancer cells invade adjacent tissue, facilitating cancer growth in different areas of the body.
3) Metastatic – the ability of cancer cells to travel to different sites in the body and invade to form new tumours.

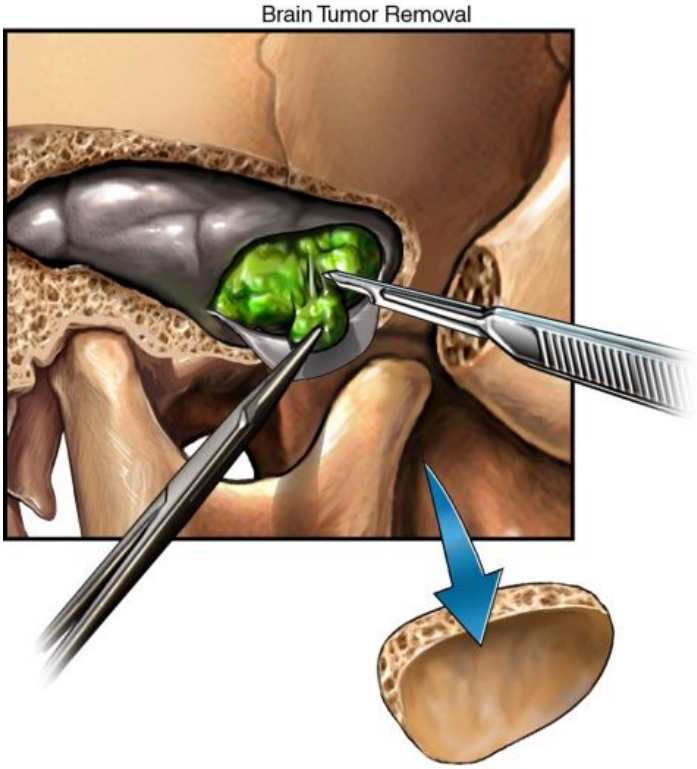


4) Immortal – Cancer cells do not die, they continually divide.

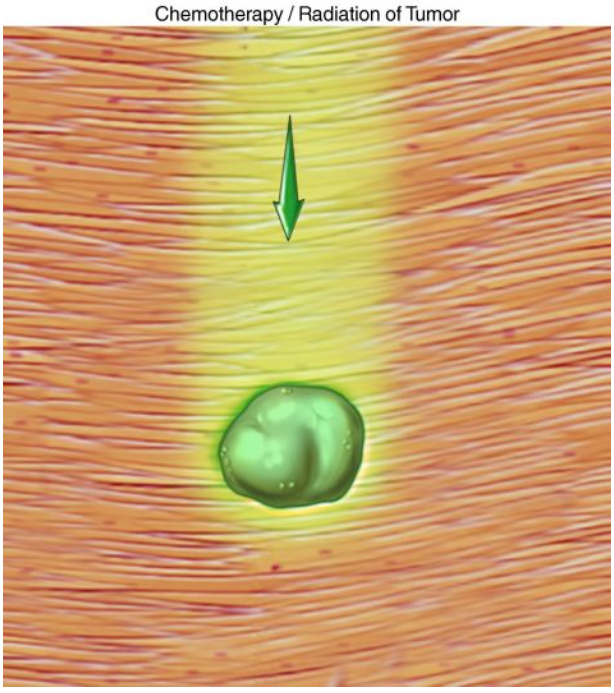
5) Angiogenesis – Cancer cells develop their own blood vessels to supply nutrients. This is a critical step to allow them to proliferate.

<u>Treatment Modalities for Cancer</u>

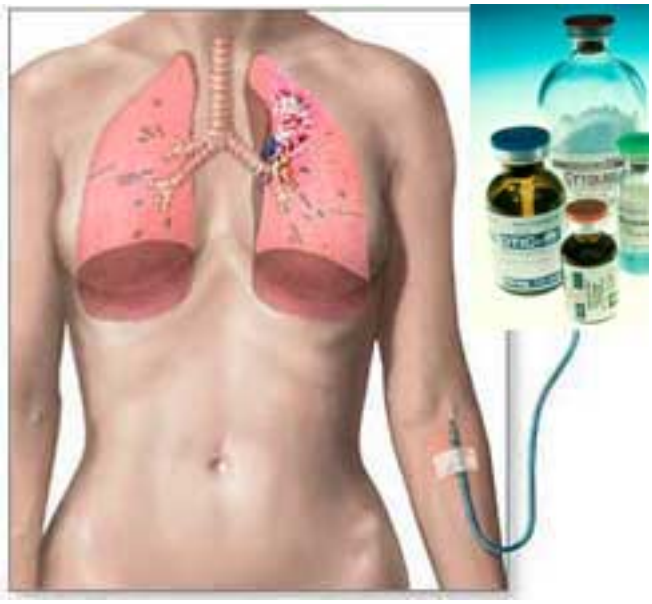
1) Surgery – the tumour is removed.



2) Radiation – high energy radiation is used to shrink tumours and kill cancer cells. Radiation therapy damages DNA of both cancerous and non-cancerous cells.

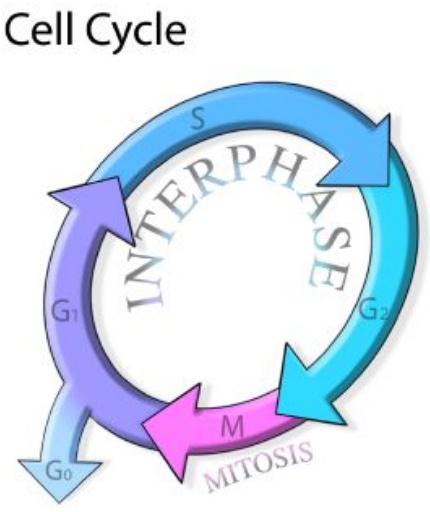


3) Chemotherapy – Drugs are used to treat cancer. As cancerous cells are dividing rapidly, chemotherapeutic drugs target rapidly dividing cells.



The Cell Cycle

- As the treatment of cancer involves targeting cell proliferation, an understanding of the cell cycle is essential for understanding the mechanism of drug action.



Phases of the Cell Cycle

G0 – Resting, cells don't replicate.

G1 – The cell prepares to synthesize (duplicate) its DNA.

S – The cell synthesizes DNA.

G2 – The cell prepares for mitosis.

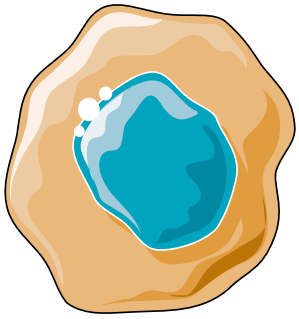
M – The cell divides in a process called mitosis.

17.2 – Obstacles to Successful Chemotherapy

Toxicity to Normal Cells

- Neoplastic cells (i.e. cancer cells) are very similar to normal cells. Therefore it is difficult to specifically target only cancer cells during chemotherapy.

NORMAL CELL



CANCEROUS CELL

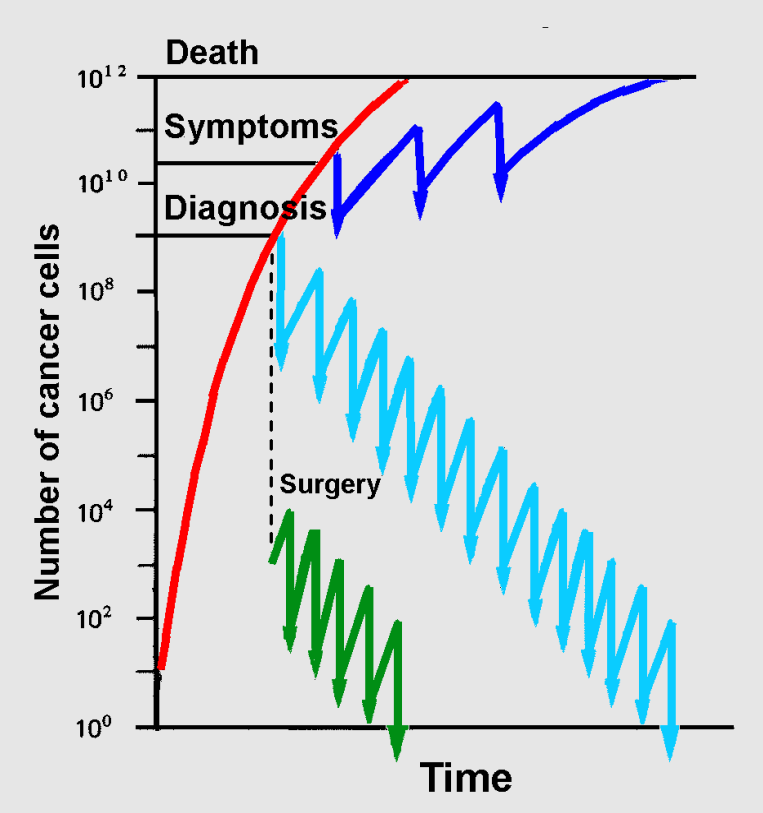
- The most cellular toxicity occurs to cells with a *high growth fraction*. The growth fraction is the ratio of proliferating cells to cells in the resting (G_0) state. Examples of cells with a high growth fraction include: bone marrow, GI epithelium, hair follicles and the germinal epithelium of the testes, that gives rise to sperm.
- Aside from killing cancer cells, chemotherapeutic drugs kill normal cells.

Cure of Cancer Requires 100% Cell Kill

- In order to cure cancer, we must kill virtually all cancerous cells in the body. This is difficult as there are not good tests to determine whether cancerous cells are present in the body in low numbers.
- The kinetics of cell death with chemotherapy are first-order. This means that a constant percentage of cancerous cells are killed at a given dose of drug.

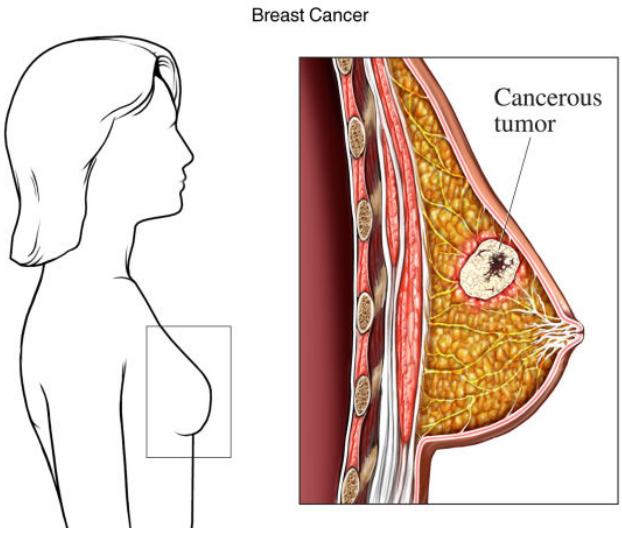
Difficult Early Detection

- Cancer is almost always significantly progressed by the time it is diagnosed.
- In the figure the red line shows the progression of the tumour growth. Notice how the tumour is not detected until there are 10^9 tumour cells.
- The dark blue line shows what happens when treatment is started late and the treatment regimen is not effective.
- The light blue line shows a better prognosis when treatment is initiated earlier and the treatment regimen is more effective.
- The green line shows how decreasing the tumour burden with surgery followed by chemotherapy can be effective if possible.

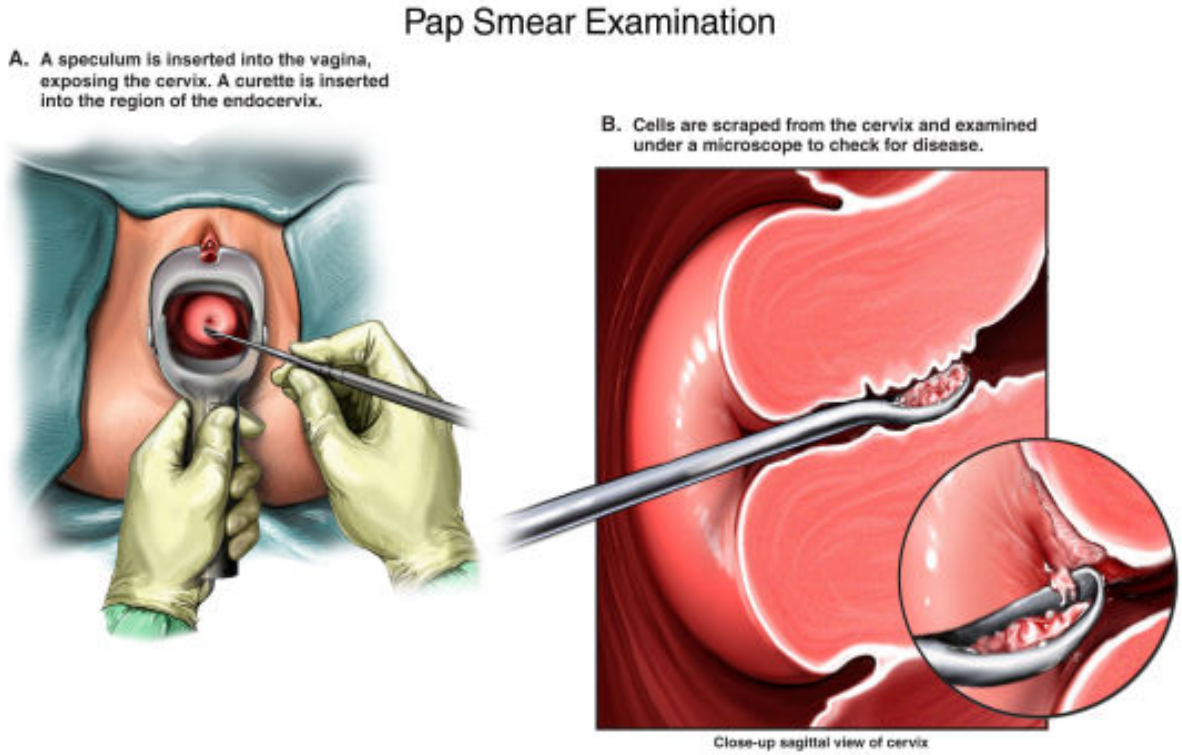


- Various cancers have screening programs established in Canada. Some of the screening guidelines (from the Canadian Cancer Society) include:

Breast Cancer – Clinical Breast Examination every 2 years for women over 40. High risk patients should be screened more often and screening may start earlier than age 40.

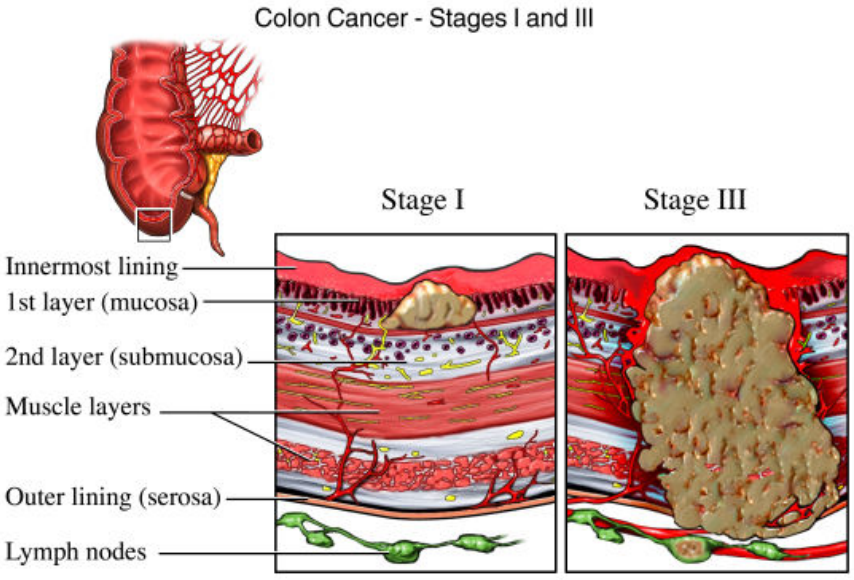


Cervical Cancer – The most important risk factor for cervical cancer is Human Papillomavirus (HPV) infection. HPV is spread primarily by genital skin-to-skin contact and it is estimated that over 75% of women AND men will have at least one HPV infection in their lifetime. Sexually active women should have a Pap test every 1-3 years.

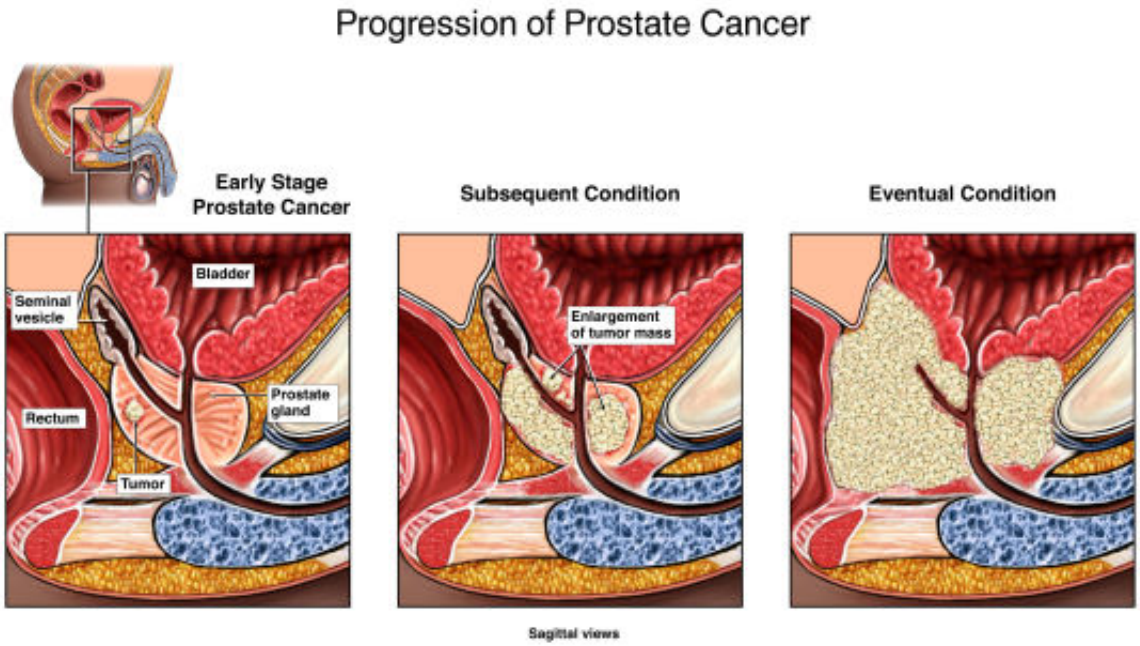


Colorectal Cancer

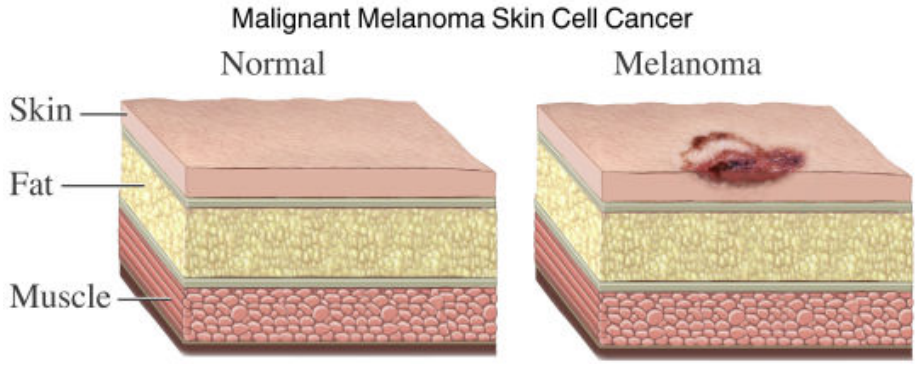
- Men and women over 50 who are not at high risk should have a fecal occult blood test every two years.
- Colonoscopy may also be performed every 5 years in high risk patients.



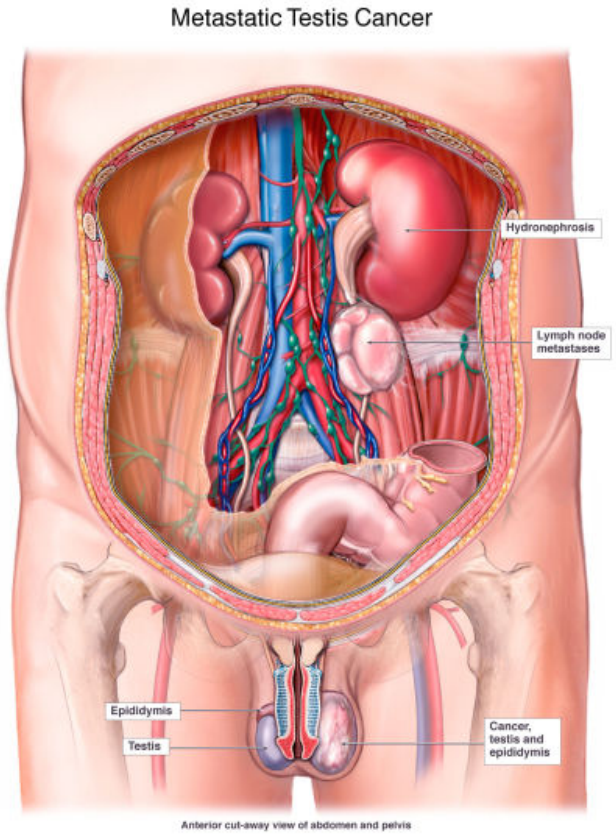
<u>Prostate Cancer</u> – Men over 50 should have the Digital Rectal Exam and/or the Prostate Specific Antigen blood test.



<u>Skin Cancer</u> – Self-checks should be performed regularly. In particular, look for changes to birthmarks and/or moles, any new skin growths, and sores that don't heal properly.

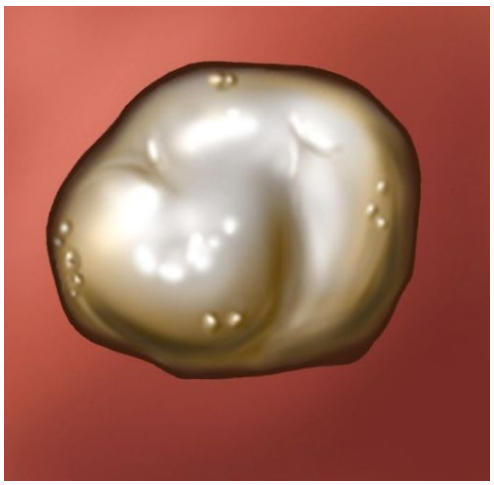


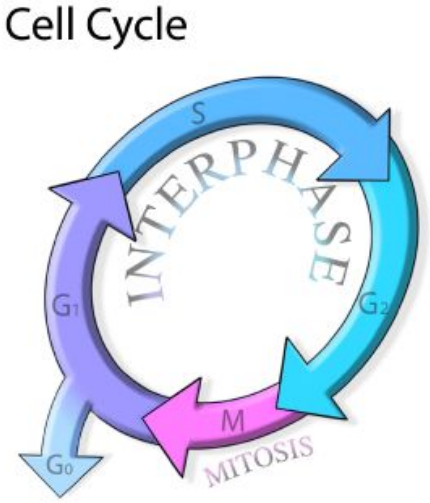
Testicular Cancer – Males over the age of 15 should regularly perform the Testicular Self Examination.



Solid Tumours Respond Poorly To Chemotherapy

- Solid tumours have a large fraction of cells in the resting (G_0) state. As most chemotherapeutic drugs target proliferating cells, solid tumours don't respond as well.

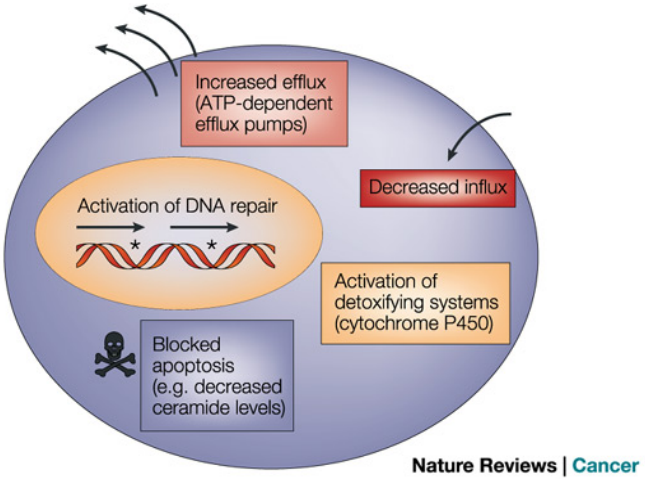




Drug Resistance

- Cells can develop resistance to drugs used during chemotherapy.
- Mechanisms of resistance can include:

1. decreased drug uptake,
2. increased drug efflux,
3. decreased drug activation (in the case of prodrugs),
4. reduced target sensitivity, increased cellular (primarily DNA) repair.
5. Decreased apoptosis (programmed cell death).

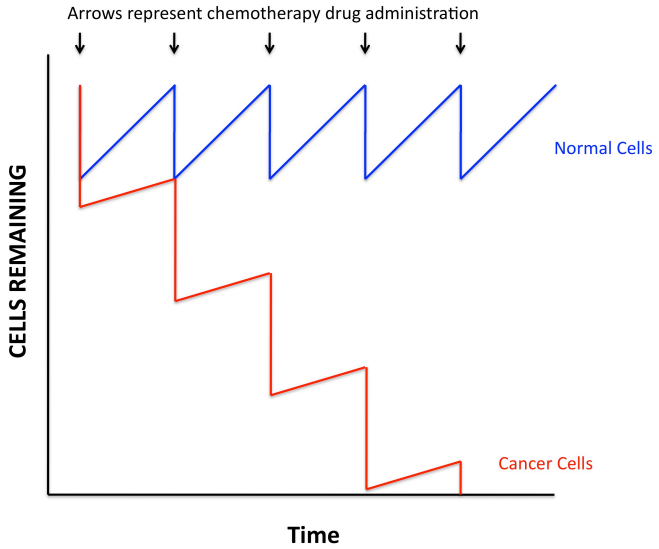


- P-glycoprotein is an efflux drug pump that pumps drugs out of cells (*remember Module 2?*). By not allowing cellular accumulation of chemotherapeutic drugs, P-glycoprotein can cause multiple drug resistance.
- Resistant cells are not killed by chemotherapeutic agents and therefore this phenomenon can cause therapeutic failure.

17.3 – Strategies to Achieve Maximum Benefit from Chemotherapy

Intermittent Chemotherapy

- The intent of this strategy is to kill cancer cells by administering chemotherapeutic drugs intermittently. This allows time for normal cells to recover.
- For this approach to be successful, normal cells must grow back faster than cancerous cells as in the example on the right.



Combination Chemotherapy

- Using a number of chemotherapeutic agents is often more effective than administering a single drug. The reasons for this include:

1) **Decreased Resistance** - Resistance may be acquired due to random mutations in cancer cells. It is unlikely that cancer cells will undergo multiple different mutations. Therefore using multiple drugs with different mechanisms of action makes therapy less likely to be affected by resistance.

2) **Increased Cancer Cell Kill** – Drugs with different mechanisms of action will kill more cancer cells than a single agent. Drugs with different mechanisms of action attack cancer cells in different ways resulting in greater cell kill.

3) **Decreased Injury to Normal Cells** – Using drugs that do not have overlapping toxicities allows us to achieve greater anti-cancer effects safely than we could with one drug alone.

17.4 – Chemotherapeutic Associated Toxicities

- Although toxicity to individual drugs may vary, there are some common and important toxicities.
- Remember toxicity typically occurs in cells with a high growth fraction.

Bone Marrow Suppression

- Bone marrow has a very high growth fraction and is therefore very susceptible to chemotherapy associated toxicity.
- Bone marrow suppression may result in:

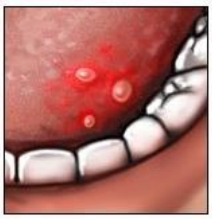
1) Neutropenia – decreased neutrophils in the blood. Neutrophils are a type of white blood cell that help the body fight infections.

2) Thrombocytopenia – decreased platelets in the blood. Platelets are involved in the coagulation (or blood clotting) process. Decreased circulating platelets increases the risk of serious bleeding events.

3) Anemia – decreased number of erythrocytes (red blood cells) in the blood. Although an important toxicity, anemia is less of a concern than neutropenia and thrombocytopenia.

Digestive Tract Injury

- Stomatitis (inflammation of the oral mucosa) may develop to some chemotherapeutic agents. If severe enough this may progress to ulceration.
- Diarrhea may occur secondary to the damage the chemotherapeutic drugs cause to the epithelial lining of the intestine.



Stomatitis

Nausea and Vomiting

- A serious and common adverse effect associated with chemotherapy. Sometimes these effects are treatment limiting and patients will refuse further treatment because of the frequency and unpleasant emetic effects of chemotherapeutic drugs.
- Anti-emetic drugs, prevention of dehydration, and prevention of malnutrition may be important adjuncts to chemotherapy.

17.5 – Drugs to Treat Cancer

- Anti-cancer drugs can be broken down into two major classes:

    1. Cytotoxic agents
    2. Hormonal and other agents

CYTOTOXIC AGENTS

- There are several different types of cytotoxic anti-cancer drugs as summarized below:

1) Alkylating agents
2) Platinum compounds
3) Antimetabolites
4) Antitumour antibiotics
5) Mitotic inhibitors

Cell Cycle Phase Specificity

- Cytotoxic drugs can be separated into either cell cycle phase specific or cell cycle phase non-specific drugs.
    - **Cell cycle phase specific drugs** are only effective if the cancer cell is in a specific phase of the cell cycle. For example, mitotic inhibitors are only effective when cancer cells are undergoing mitosis. Phase specific drugs are only effective in cells that are actively part of the cell cycle and are ineffective for cells that are in Go.

    - **Cell cycle phase non-specific drugs** can act during any stage of the cell cycle including Go. Although phase non-specific drugs are effective at any stage of the cell cycle, they are more toxic to cells that are proliferating than to cells in Go.

1) Alkylating Agents

- Are highly reactive chemicals that act by transferring an alkyl group to cell components (primarily DNA).
- They act by forming cross-bridges between nitrogen atoms on guanine nucleotides that make up our DNA.
- The result of treatment with alkylating agents is miscoding, breaking of DNA, and possibly inhibition of DNA replication.
- Alkylating agents are cell-cycle phase non-specific, meaning they may be effective during any phase of the cell cycle.
- Cyclophosphamide is the most widely used drug in this class. Cyclophosphamide is a prodrug and must be converted to its active form by the liver. For this reason its onset of effect is often delayed.
- Common indications for cyclophosphamide include Hodgkins disease and solid tumours of the head, neck, ovary and breast.

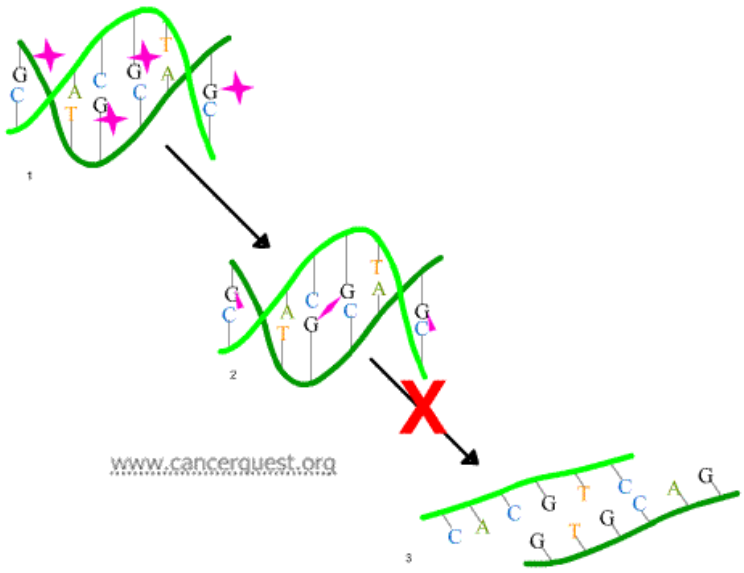
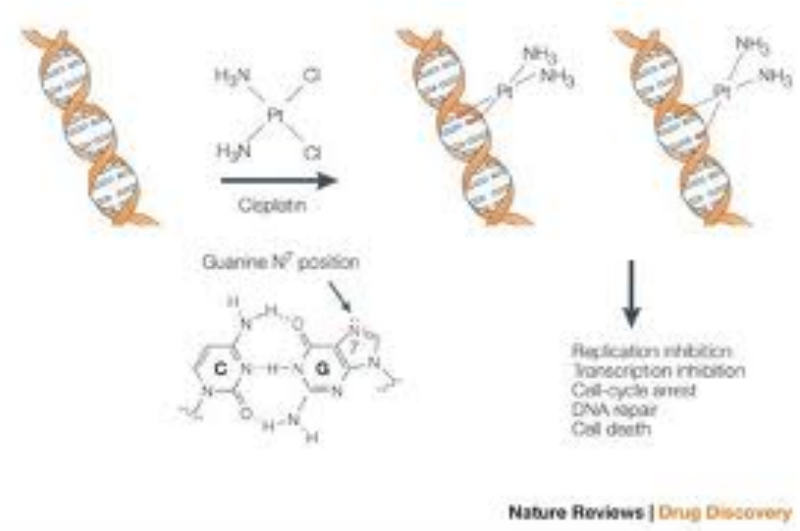


Figure: Mechanism of action of alkylating agents. Alkylating agents (pink molecules) bind to nitrogen residues of guanine nucleotides. This may result in cross-linking of DNA.

2) Platinum Compounds

- Are drugs with platinum in their chemical structure.
- Act by cross-linking DNA and therefore inhibiting DNA replication.
- They cross-link DNA by binding to guanine nucleotides, similar to alkylating agents.
- Are cell-cycle phase non-specific.
- Cisplatin is the most widely used platinum compound, and is used in the treatment of metastatic ovarian and testicular cancers as well as advanced bladder cancer.
- Cisplatin is extremely nephrotoxic, ototoxic (toxic to the ear and may cause deafness) and emetogenic (causes nausea and vomiting).



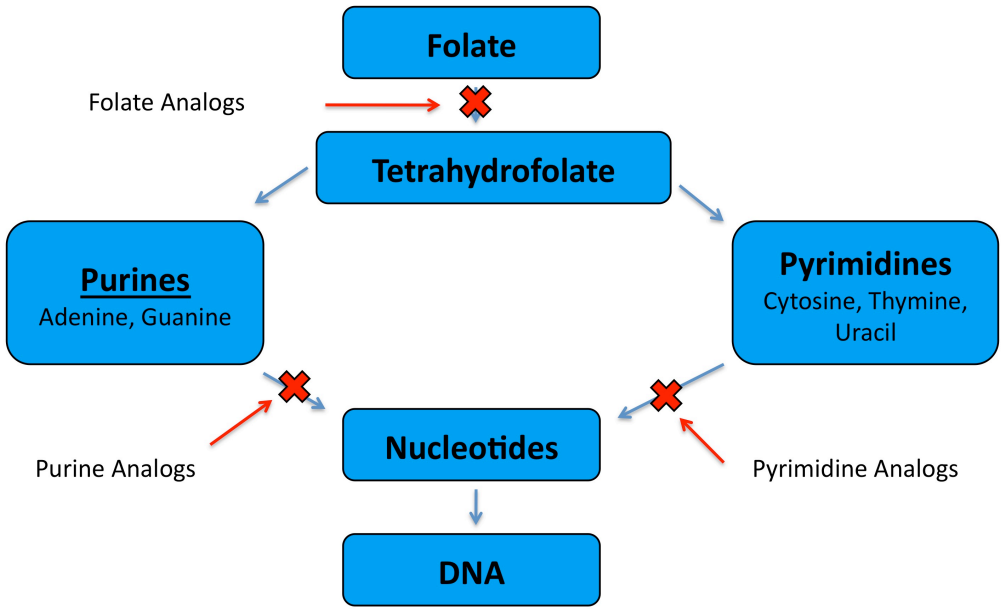
3) Antimetabolites

- Are structurally similar to natural compounds the body uses to: a) synthesize cellular constituents or b) incorporate into DNA.
- They act by inhibiting particular enzymes or by preventing DNA replication.
- Antimetabolites are phase specific and most (although not all) act during S-phase.
- Antimetabolites can be further classified into 3 subclasses:

1) Folic acid Analogs – block the conversion of folate to its active form.

2) Purine Analogs – purines are used to make DNA and RNA. Purine analogs inhibit the synthesis of DNA and RNA.

3) Pyrimidine Analogs – pyrimidines are used to make DNA and RNA. Pyrimidine analogs inhibit the synthesis of DNA and RNA.



4) Antitumour Antibiotics

- Kill cancer cells by intercalating DNA. This means that they move between the bases of DNA and bind to DNA. This causes a change in the structure of DNA. The altered DNA structure is unable to be used as a template by DNA polymerase and therefore DNA synthesis is inhibited.
- Antitumour antibiotics are very poorly absorbed and therefore are given intravenously.

Anthracyclines

- Are a type of antitumour antibiotic.
- Although they are effective and widely used chemotherapeutic agents, anthracyclines can cause severe bone marrow suppression and are cardiotoxic (toxic to the heart).

5) Mitotic Inhibitors

- Act during the cell cycle to inhibit mitosis and therefore prevent cell division.
- Are separated into 2 different subclasses: vinca alkaloids and taxanes.

1) Vinca Alkaloids – are derived from the periwinkle plant.

    - Block the process of mitosis during metaphase.
    - They block metaphase by binding to the protein tubulin, a major component of the microtubule. This disrupts the organization of microtubules during cell division and leads to inappropriate distribution of chromosomes and eventually cell death.

2) Taxanes

    - Act in the late G2 phase of the cell cycle, just prior to mitosis.
    - Taxanes stabilize microtubule bundles and therefore prevent cell division.

HORMONAL AGENTS

1) Glucocorticoids

- Are used as an adjunct to other chemotherapeutic agents in cancers that are derived from lymphoid tissue.
- Are beneficial because they are directly toxic to lymphoid tissue.
- Side effects from long term use include osteoporosis, adrenal insufficiency, susceptibility to infection, GI ulceration, electrolyte disturbance and growth retardation.
- Can also be helpful in management of complications of other chemotherapy drugs including reduction in nausea and vomiting, reduction of pain, and improved appetite.

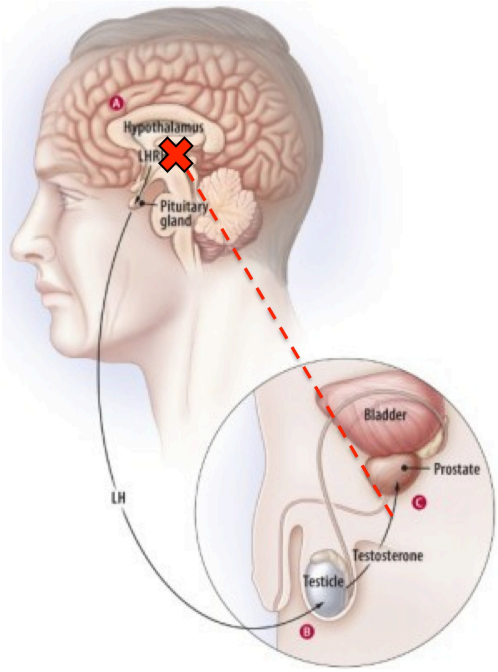
2) Drugs for Prostate Cancer

- Prostate tissue (normal and neoplastic) is androgen dependent and therefore the primary goal in the treatment of prostate cancer is androgen (i.e. testosterone) deprivation.

- Androgen deprivation can be achieved by:

1. Gonadotropin Releasing Hormone (GnRH) agonist or surgically by castration.
   - GnRH agonists cause a transient increase in testosterone production in the testes, so cancer symptoms may increase at the start of therapy.
   - Over time, testosterone synthesis and release is decreased.

2. Androgen Receptor Antagonists
   - Used in combination with a Gonadotropin Releasing Hormone agonist or castration.
   - Act by blocking androgen receptors in tumour cells.



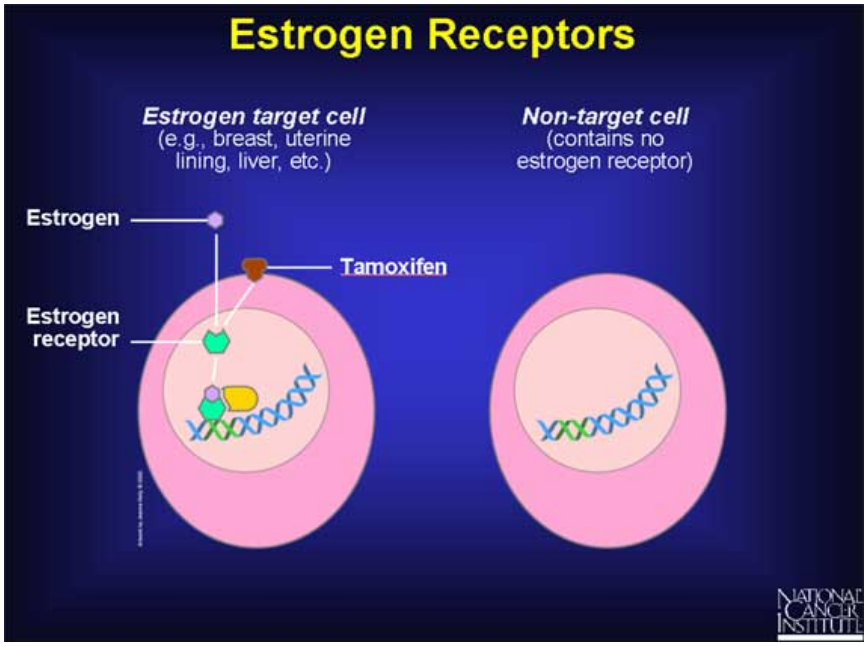
• GnRH (here shown as LHRH) causes release of testosterone from the testes.
• Testosterone "feeds" prostate cancer cells but also acts by negative feedback to inhibit further GnRH release.
• GnRH agonists cause a transient increase in testosterone but then cause decreased GnRH activity through desensitization and negative feedback.
• The net effect is decreased testosterone synthesis and release.

3) Drugs for Breast Cancer

- Breast cancer is the most common cancer affecting women.
- Estrogen causes breast tumour cells to proliferate.
- Depriving breast cancer cells of estrogen is the primary pharmacological treatment of breast cancer.
- It should be noted the estrogen receptor antagonism is used as an adjunct to surgery and radiation therapy.
- Pharmacological treatment of breast cancer can be divided into three major classes 1) The anti-estrogens, 2) aromatase inhibitors and 3) Trastuzumab.

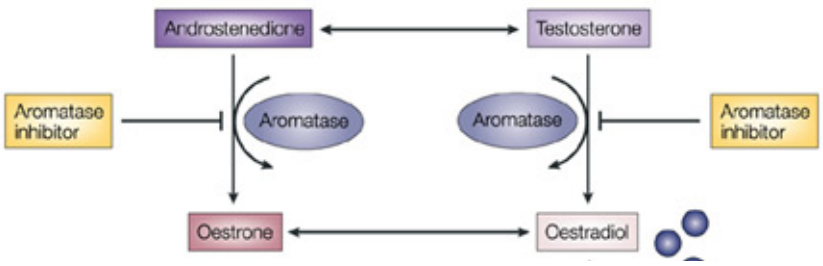
1) Anti-estrogens – block estrogen receptors.

- The most commonly prescribed drug for breast cancer is tamoxifen.
- Tamoxifen is a partial estrogen receptor agonist meaning that it minimally activates the estrogen receptor but also blocks endogenous estrogen from binding to its receptor (*remember Module 7?*). The net effect of tamoxifen is blocking the binding of endogenous estrogen to the estrogen receptor.



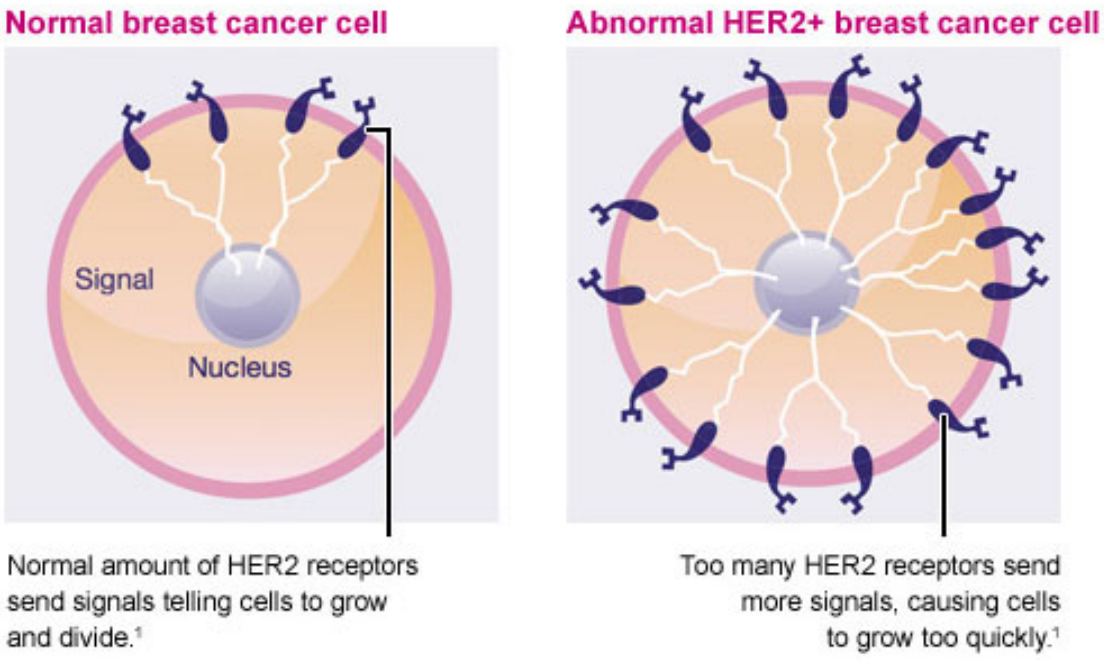
2) Aromatase Inhibitors

- Aromatization is the process of converting androgens into estrogen.
- Aromatase inhibitors inhibit the conversion of androgens to estrogens, and therefore decrease the amount of estrogen available to breast cancer cells.
- It is important to note that aromatase inhibitors do not block ovarian estrogen synthesis, and therefore aromatase inhibitors are only useful in postmenopausal women.



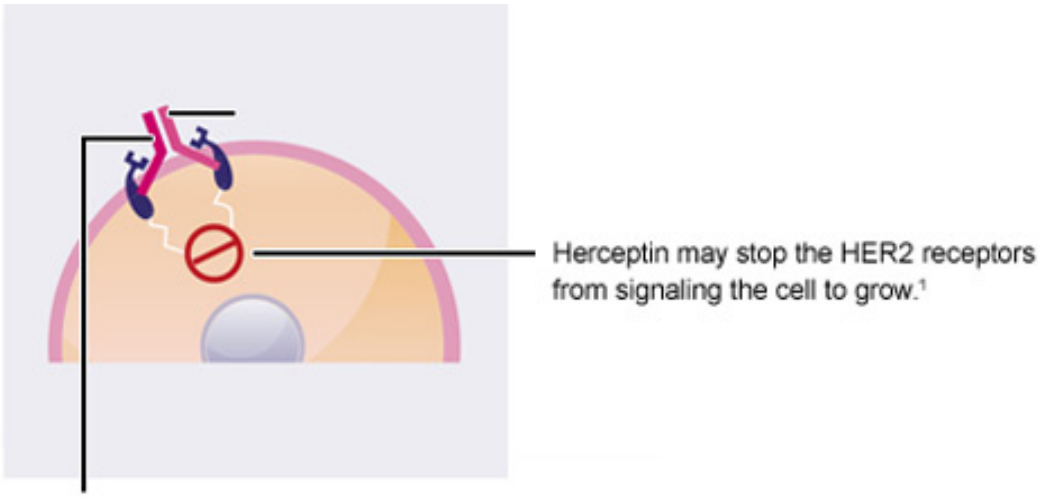
3) Trastuzumab

- Some patients with breast cancer have an increased number of human epidermal growth factor receptor 2 (HER2).
- HER2 is a transmembrane receptor that helps regulate cell growth.
- Tumours with increased HER2 have especially aggressive tumour growth.



- Trastuzumab is a monoclonal antibody that binds to HER2 and prevents cell proliferation.
- As trastuzumab is an antibody, it must be administered intravenously (antibodies are degraded in the stomach and poorly absorbed).
- The most prominent adverse event is cardiotoxicity.

Mechanism of action of Trastuzumab (marketed as Herceptin)



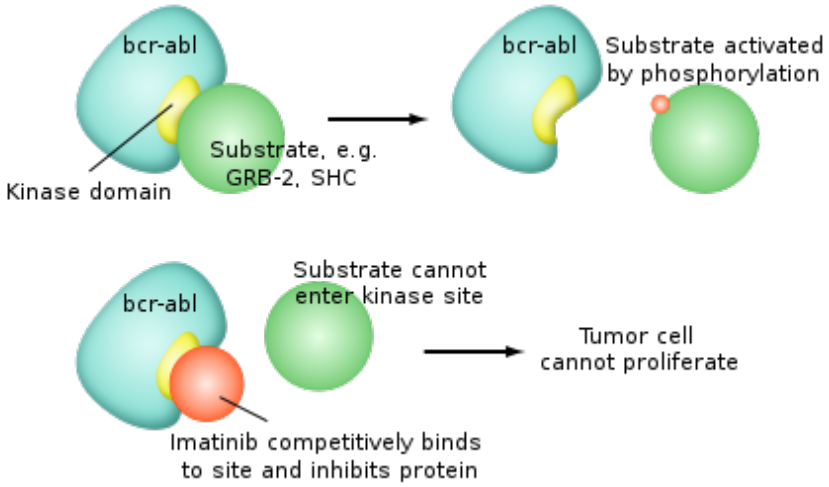
OTHER ANTICANCER DRUGS

Tyrosine Kinase Inhibitors

- Protein kinases are enzymes that phosphorylate proteins on specific amino acid residues (i.e. tyrosine).
- Activity of tyrosine kinases can activate gene transcription and/or DNA synthesis, therefore making them an attractive option for the treatment of cancer.
- Increased activity of tyrosine kinases has been observed in many human cancers.

Imatinib

1. Is the prototype tyrosine kinase inhibitor.
2. Effective in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumours (GIST).
3. Causes complete inhibition of cellular proliferation and cell death via apoptosis (programmed cell death).
4. Primary toxicities include nausea, vomiting, edema, and muscle cramps.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Kinase domain
Substrate, e.g.
GRB-2, SHC
bcr-abl
Substrate activated
by phosphorylation
bcr-abl
Substrate cannot
enter kinase site
Tumor cell
cannot proliferate
Imatinib competitively binds
to site and inhibits protein