Lecture 7: Carcinogenesis

Oncology: The science and medical specialty of cancer and cancer treatments

Anti-cancer (oncology agents): These are the most dangerous of drugs, other than perhaps the narcotic analgesics. This is due to their toxicities. Killing or inhibiting cancer cells is very challenging. Although cancer cells are abnormal, they are still human, so achieving selectivity is critical. Cytotoxic agents kill cancer cells. Cytostatic agents inhibit the growth of cancer cells.

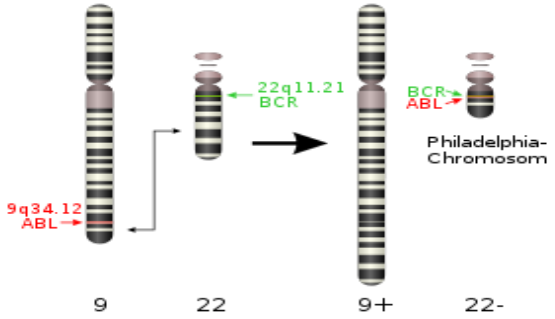
Carcinogenesis: Under normal circumstances cells in the human body are under strict control in terms of growth and differentiation. This growth and differentiation is stimulated by growth factors. Cell growth can temporarily cease (senescence), and cells can also undergo organized and programmed cell death (apoptosis). Apoptosis is a normal aspect of tissue health and maintenance. However, in cancer cells the control mechanisms have gone awry and cell growth spins out of control. The hallmark of cancer is uncontrolled growth of abnormal cells which consume nutrients and energy within the host. In addition, the cancer cells lose their ability to perform their normal functions. If the cancer cells reside in tissues, they are commonly called "solid tumors". If they involve cells in the blood, they are called "liquid tumors".

Mutagenesis: Mutations are changes in genes within DNA. Mutations can occur in proto-oncogenes to create oncogenes (which promote cancer), or mutations can occur in tumor suppressor genes (which suppress cancer). Oncogenes promote cancers and regulate the communication between cells and their outside environment. Mutations can occur in a variety of ways including inherited germ line mutations, spontaneous point mutations, chromosomal rearrangements, or through augmentation of gene expression (Table 1). After the mutations occur and generate oncogenes (or dysfunctional tumor suppressor genes), the cells that possess these mutations can be stimulated by chemical, hormonal, and viral mechanisms to promote the incorrect expression of specific proteins and the growth of the cancer cells.

Table 1: The genetic origin of several types of cancer

Cancer type	**Oncogene or tumor suppressors***
Chronic myelogenous leukemia (CML)	*bcr-abl* translocation (Philadelphia chromosome)
Follicular lymphoma	*bcl-2* amplification
Sporadic thyroid cancer	*ret* mutation
Colorectal and gastric cancer	*APC* mutation*
Familial breast, ovarian cancer, prostate	*BRCA1* and *BRCA2* mutations*
Invasive ductal breast cancer	*HER-2* amplification
Familial melanoma	*CDKN2A (p16 INK4)* mutation*
Childhood neuroblastoma, small cell lung cancer	*N-myc* amplification
Leukemia, breast, colon, gastric, and lung cancer	*c-MYC* amplification
Renal cell cancer	*VHL* mutation*
Prostate, gliobastoma, endometrial cancer	PTEN*

Figure 1. Generation of the Philadelphia chromosome by the bcr-abl translocation

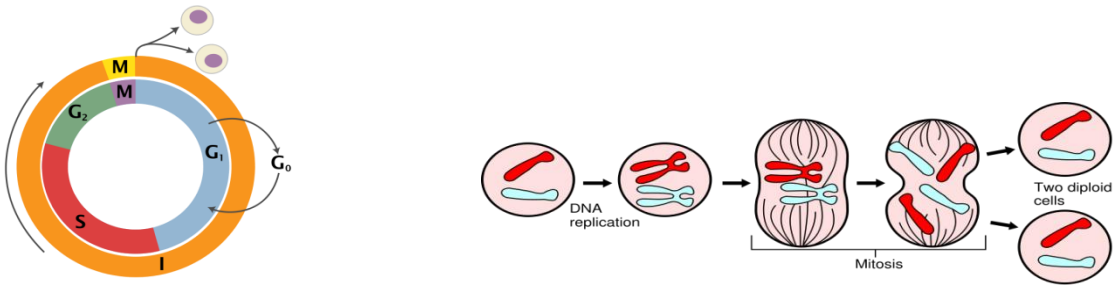


Tumor suppressor genes are the opposite of oncogenes. They exist to keep oncogenes in check (Table 1). So while the expression of oncogenes can induce cancer (gain-of-function), the inactivation or suppression of tumor suppressor genes can also induce cancer (loss-of-function, loss of protection). Two additional tumor suppressors are p53 (protein 53) and pRb (protein of retinoblastoma). Both of these proteins exert control over the cell cycle so that the cycle does not continue endlessly leading to carcinogenesis.

Cell cycle: The process whereby somatic (not sperm or egg cells) cells divide. The overall process is called mitosis and it is tightly controlled under normal circumstances (Figure 2).

G0: resting phase (most cells in the body at any one point in time)
G1: initial phase of mitosis; synthesis of enzymes required for DNA synthesis (~20 hrs)
S: DNA synthesis and replication of DNA (~20 hrs)
G2: Synthesis of RNA, protein and formation of mitotic spindle for duplication of the cell (2-10 hrs)
M: Mitosis, i.e. cell division (~1 hr); note the short timeframe for mitosis event

Figure 2: The mitotic cell cycle performs cell duplication



(Stem cells also undergo mitosis, but they are undifferentiated cells/early stage cells that can be totipotent, pluripotent, multipotent, oligopotent, or unipotent.)

It is worth noting that some (but not all) anti-cancer agents are specific for a certain phase of the cell cycle. Hence, they are called cell-cycle specific. Antimetabolites damage cells mainly in the S phase while the antimitotic agents have their greatest impact in the M phase. By combining drugs that work at different phases of the cell cycle, greater cell kill is theoretically possible. This is one reason that drug combinations are used (see polytherapy below).

Apoptosis: Also called programmed cell death. It is the orderly death of normal cells so that old and damaged cells can be replaced by new cells. Apoptosis can be accelerated by some drugs.

Necrosis: The non-orderly death of cells that is caused more immediately by a variety of insults such toxins, radiations, and drugs. Necrosis is caused by many older cancer drugs.

Metastasis: The process by which cancer cells leave the location of the parent tumor and spread to distant sites is called metastasis. The bloodstream and lymphatic system are the primary distributors of cancer cells that have sloughed from the parent tumor. It is important to note that metastases play an important role in the morbidity of late stage cancer, and many therapeutic treatments become aimed at these metastatic lesions. It is fair (and important) to say that most cancer patients die from the consequences of metastatic lesions rather than the parent tumor itself. In recent years, much research has taken aim at the tumor cells that are sloughed from primary cancer tissues. One type is called circulating tumor cells (CTCs). CTCs have been identified in the blood circulation of many different types of cancers. The measurement of CTCs has also been used as a prognostic factor (how slow or fast a patient's disease will progress) and a diagnostic factor (how well a patient is responding to a given therapy or drug). CTCs were first proven of use for metastatic treating breast cancer.

Chemotherapy: One of the major forms of therapy for the treatment of cancer. The others are surgery, radiotherapy and cell transplantation (BMT or SCT). Other forms exist of course. Needless to say, when a cancer spreads (metastasis) and becomes systemic, surgery cannot be effective. Also, radiotherapy cannot reach cancer cells that reside deep within tissues. BMT and SCT are of greatest use against liquid cancers.

Cancer cells are not "intelligent" but they are "adaptive". They survive by clonal selection (see drug resistance below) and they use many mechanisms to survive. Therefore, use of drug combinations (polytherapy) is very common in the treatment of cancer. It has become rare that any cancer is treated with a single agent or single approach. Early stage cancers that are dependent on hormones (early breast or prostate cancer) are examples where single agent therapy can be effective for a period of time. Then combinations or harsher agents are used.

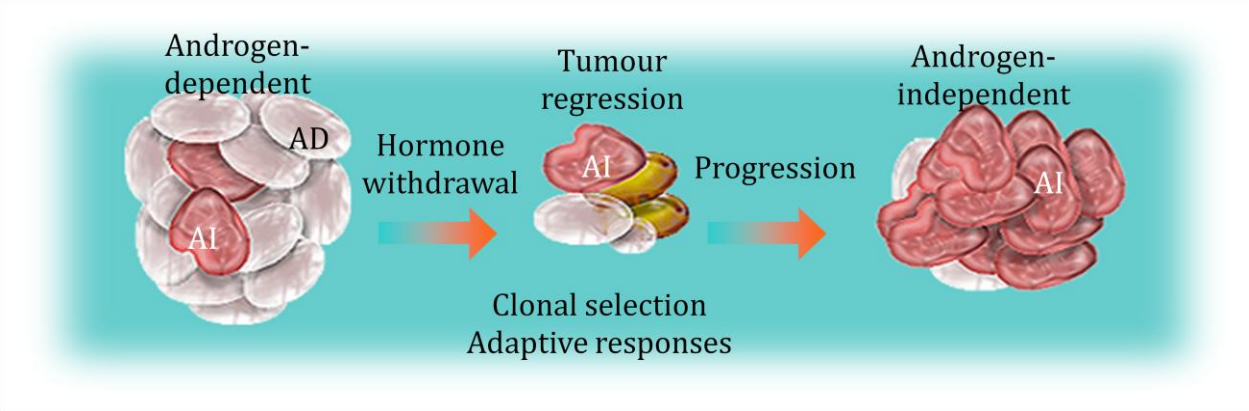
Premedications: When administering some agents there is the need to minimize the occurrence of side effects such as hypersensitivity reactions. Premedications to prevent hypersensitivity commonly involve:

- An H_1 antagonist (e.g. diphenhydramine 50 mg orally or equivalent)
- An H_2 antagonist (e.g. ranitidine 150 - 300 mg orally or equivalent)
- Corticosteroids (e.g. dexamethasone 20 mg intravenously, 30 minutes before infusion or orally, 60 minutes before infusion) in addition to pretreatment with H_1 and H_2 antagonists

Also because many anti-cancer drugs cause nausea and vomiting, antiemetics are commonly given as premedications.

Drug resistance: Cancer cells can often become resistant to the effects of drugs through a process similar to the process that bacteria become resistant to the effects of antibiotics. This is because not all cancer cells in a given tumor are exactly alike. Those cells most sensitive to the initially used drugs die, but the resistant cells survive and continue to grow and replicate in a process called clonal selection (Figure 3). This is another reason why cancer chemotherapy is often changed during the course of managing a patient's disease. The cells change.

Figure 3. Illustration of drug resistance occurring through clonal selection in prostate cancer; Androgen dependent (AD) cells are shown in grey, while androgen-independent (AI) cells are shown in red



Cancer staging: It is useful to be able to describe and communicate the severity of disease and the TNM system has been devised for solid tumors. T stands for tumor size (T1 – T4), N stands for lymph nodes (N0 – N4), and M indicate whether metastasis has occurred (M0 – M1). Taken together, the TNM criteria can be translated into stages I-IV. Stage I is localized disease, stage II and III are intermediate, and stage IV is metastatic disease. Disease staging is an important element in determining prognosis and for determining the appropriate treatment selection and dosing regimen.

Response criteria: Responses to cancer therapies are described by several categories. This is very important for decisions regarding continuation or discontinuation of various treatments. It is also very important in a research institution like the UW which is involved in clinical trial

testing of new agents. It is necessary to have meaningful criteria to compare the new agents to existing therapies. For early phase trials (Phases 1 and 2), these categories include:

Complete response (CR): A patient has no sign of cancer 1 month after completion of therapy

Partial response (PR): A patient has a reduced tumor size of 30% or more (at 1 month)

Stable disease (SD): A patient's tumor size has not increased more than 20% and decreased less than 30% (at 1 month)

Progression (P): A patient's tumor has grown more than 20% or there is formation of new lesions (at 1 month)

There is beginning to be use of CTCs to measure response along with the above response criteria, but this is not yet widely accepted. Used as such, measurements of CTCs are a type of surrogate marker that are starting to be of use to monitor tumor growth and initial response to therapy. Additional new markers (specific genes or proteins) will be more important in the future because they can be easier, faster, and more precise than measuring tumor size.

For the final stage of clinical trial evaluation (Phase III), the primary endpoints typically concern survival:

Overall survival (OS): Simply the measurement of how much longer do patients survive (on average); historically OS has been the gold standard for measuring new drug effectiveness

Progression free survival (PFS): Measurement of how much longer patients survive without progression (worsening) of the disease

Personnel: Modern care of cancer patients typically involves a team of medical experts. These include surgical oncologists, radiation oncologists, hematologic oncologists, medical oncologists, oncology pharmacists, oncology nurses, oncology histopathologists, and geneticists. Medical oncologists are responsible for selecting and guiding the administration of oncology agents. Oncology pharmacists play important roles on the team with the medical oncologists and oncology nurses in terms of drug preparation and formulations. Oncology pharmacists should also pay attention to drug interactions and combined toxicities. Depending on the setting, the oncology pharmacist could be the one explaining the most details about drug interactions and toxicities to patients.

Clinical trials: Clinical trials are critically important to the development of new anti-cancer drugs. The process occurs in three stages (Phase 1, Phase 2 and Phase 3). Phase 1 trials focus on characterizing the pharmacokinetics and dose-limiting toxicities of any new agent. Phase 2 focuses on demonstrating sign(s) of efficacy in specific cancer types. Phase 3 focuses on definitive proof of efficacy as well as the type and frequency of side effects in a well selected group of patients. Clinical trials are important activities at research universities such as the UW.

Visit www.clinicaltrials.gov for a searchable website of ongoing clinical trials in the U.S. and with clinical sites outside the U.S. Finally, patients themselves are also very important to the conduct of clinical trials – without them trials cannot be done.

FDA: The Food and Drug Administration is the federal regulatory agency that regulates the drug development process. FDA is constantly updating its regulations and guidelines to help industry develop safe and effective new drugs. Drug approvals and withdrawals are issued by FDA. FDA and companies discuss/debate the language that goes into the package inserts for drugs. Of course, the package inserts describe exactly what the drug can be used for, how it is to be used, side effects, etc. The package insert is the definitive source of information about a drug.

Cancer incidence in the U.S.: The big four cancers in terms of incidence are breast cancer, colorectal cancer, lung cancer, prostate cancer. Best source of cancer incidence and mortality is provided by the American Cancer Society.

http://www.cancer.org

Most lethal cancers in U.S.: Esophageal, glioblastoma (type of brain cancer), liver & bile duct, and pancreatic. There are other very rare cancers that have high mortality. Part of the explanation for the high mortality in rare disease is that it is difficult (or impossible) to conduct the necessary clinical studies if few patients exist. Conversely, we know a great deal about breast cancer because this cancer is not rare in women and women tend to be very good enrollers in clinical trials (historically better than men). In recent years, we now know much more about colorectal, lung, and prostate cancer due to better enrollment in clinical trials.

Personalized/precision medicine: Use of genotype and phenotype information to guide the administration of drugs to patients on an individual basis. This approach is rapidly advancing in the field of medical oncology, probably faster than in any other field of medicine. Note the challenge of trying to do clinical trials with new drugs or therapies that are customized to each single patient. It is difficult or impossible to get adequate statistical power in such small studies. FDA is very aware of this challenge and is working closely with companies in such cases.