Lecture 1: Carcinogenesis

Anti-cancer (oncology agents): These are perhaps the most dangerous of drugs, other than 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 of cells 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 goes 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 are 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 of 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, environmental, 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.

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<thead>
<tr>
<th>Cancer type</th>
<th>Oncogene or tumor suppressors*</th>
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<tr>
<td>Chronic myelogenous leukemia (CML)</td>
<td>bcr-abl translocation (Philadelphia chromosome)</td>
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<tr>
<td>Follicular lymphoma</td>
<td>bcl-2 amplification</td>
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<tr>
<td>Sporadic thyroid cancer</td>
<td>ret mutation</td>
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<tr>
<td>Colorectal and gastric cancer</td>
<td>APC mutation*</td>
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<tr>
<td>Familial breast and ovarian cancer (prostate)</td>
<td>BRCA1 and BRCA2 mutations*</td>
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<td>Invasive ductal breast cancer</td>
<td>HER-2 amplification</td>
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<tr>
<td>Familial melanoma</td>
<td>CDKN2A (p16 INK4) mutation*</td>
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<tr>
<td>Childhood neuroblastoma, small cell lung cancer</td>
<td>N-myc amplification</td>
</tr>
<tr>
<td>Leukemia, breast, colon, gastric, and lung cancer</td>
<td>c-MYC amplification</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>VHL mutation*</td>
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<tr>
<td>Prostate, glioblastoma, endometrial cancer</td>
<td>PTEN*</td>
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*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 \textbf{inactivation} or suppression of tumor suppressor genes can also induce cancer (loss-of-function). 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.

**Cell cycle:** The process whereby \textit{somatic} (not sperm or egg cells) cells divide. The overall process is called \textbf{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

\textbf{Figure 2:} The mitotic cell cycle.
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. As one might expect, 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 to say that most cancer patients die from the consequences of metastatic lesions rather than the parent tumor. 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).

Chemotherapy: One of the three major forms of therapy for the treatment of cancer. The other two forms are surgery and radiotherapy. 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. Cancer cells are not “intelligent” but they are “adaptive”. They survive by clonal selection (see 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. Early stage cancers that are dependent on hormones (early breast or prostate cancer) are examples where single agent therapy can be effective.

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\textsubscript{1} antagonist (e.g. diphenhydramine 50 mg orally or equivalent)
- An H\textsubscript{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\textsubscript{1} and H\textsubscript{2} antagonists.

Also because many anti-cancer drugs cause nausea and vomiting, antiemetics are also 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.

**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. 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 as it is necessary 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

**Stable disease** (SD): a patient’s tumor size has not increased more than 20% and decreased less than 30%

**Progression** (P): a patient’s tumor has grown more than 20% or there is formation of new lesions

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 **biomarker** or **surrogate marker** that are starting to be used to monitor tumor growth or 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)

**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 an important role on the team with the medical oncologists and oncology nurses. Oncology pharmacists should pay attention to drug interactions and combined toxicities.

**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**. Clinical trials are important activities at research universities such as the UW. Visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for a searchable website of ongoing clinical trials in the U.S. **Patients** are also very important to the conduct of clinical trials – without them trials cannot be done.
FDA: 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 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).

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.