The Biology of Cancer – Week 6 Notes

* Treatment Overview

Treatments are different if cancers are localized and curable vs metastasized.

* Types of Treatment

There are many treatment types:

1. Surgery
2. Radiation
3. Hormonal Therapy
4. Chemotherapy
5. Targeted Therapy
6. Immunotherapy

Appox 50% of all people diagnosed with cancer in the US are cured by surgery or radiation because the cancer is removed or killed by radiation before it has spread.

There therapies provide the backbone for all cancer therapy: surgery removes the tumor, radiation can be given as external beam radiation or by implanting radioactive seeds into the tumor.

External beam radiation therapy – usually given in several doses or fractions over time. Can be equally as curative as surgery. And in many cases, when you have a small, primary cancer, physicians give the patient the option of being treated with surgery or radiation for definitive cure.

Radiation can also be used for palliation, to simply shrink a tumor that is causing pain or some other problem in the body. And when it’s not given as curative intent, it’s called palliative radiation.

How does radiation work? It works by killing dividing cells through DNA damage which leads to cell death. So when the radiation hits your DNA, the DNA is damaged, that is recognized by the cell as not normal and the cell undergoes a programmed cell death. (apoptosis)

When surgery or radiation are used as the primary therapy to try and cure a cancer, sometimes other therapies like chemotherapy are given around the time of the surgery of radiation. If that therapy is given before, it’s called neoadjuvant therapy. If given after, it’s called adjuvant therapy. These terms apply, it does not matter what cancer you are talking about.

What are the various therapies? One is based on hormones. Hormones tell various organs what to do. Estrogen/testosterone. Hormones can also stimulate cancer.

Estrogen stimulates breast cancer growth and ant-estrogen agents are used to help treat breast cancer.

Testosterone stimulates prostate cancer growth. Anti-testosterone agents are used to treat prostate cancer.

Chemotherapy works differently. Almost all chemo have been designed to keep cells from dividing. Cancer cells tend to divide more rapidly than normal cells and , therefore, they are more likely to die from treatment.

Normal cells in the body, like cells in hair follicles, white blood cells that fight infection, and cells in the lining of the colon, are also dividing, and that is why the main side effects of chemo are hair loss, infection risk, and nausea/diarrhea.

There are two broad classes of chemo agents.  
1.) Agents that interfere with replication of DNA  
2.) Agents that interefere with cell division by blocking mitosis.

Inhibiting replication of DNA – Several targets, therefore several classes of drugs to inhibit replication.   
-Anti-metabolites: base pair drugs that are intercalated into the DNA strand and prevent replication.  
-Topoisomerase unwinds DNA for replication, and then repacks it. Topoisomerase inhibitors target this process.   
- Broad group of DNA intercalators that include metals, alkylators, and antibiotics that all intercalate into the DNA strange, and prevent it from reproducing itself correctly.

Agents that interefere with DNA replication:

1. Metals: platinum agents, cisplatin, carboplatin, oxaliplatin
2. Anti-metabolites: 5-fluorouracil (5FU), capecitabine (Xeloda), gemcitabine (Gemzar), pemetrexed (Alimta).
3. Alkylators: cyclophosphamide (Cytoxan) – most famous
4. Antibiotics: Doxorubicin (Doxil) - most famous, most widely used
   1. Topoisomerase inhibitors – etoposide (VP-16), irinotecan (Camptosar)

Agents that interfere with Cell Division:  
1.) Inhibition of microtubules, preven the migration of chromosomes to daughter cells. Vinorelbine, taxol, etc.

Targeted Therapy: This inhibits proteins that are mutated or overexpressed and helping the cancer to grow. This makes the therapy more “cancer specific.” This should not causing as many side effects with less specific therapy.   
1.) VEGF (vascular endotheliam growth factor). Bevacizumab (Avastin), Cyramza  
2.) EGFR (epidermal growth factor receptor). Tarceva, Afatinib, Iressa, Erbitux  
3.) HER2: Herceptin, Perjeta, Kadcyla, Tykerb  
4.) ALK [oncogene] (anaplastic lymphoma kinase): Xalkori  
5.) mTOR (mechanistic target of rapamycin) Afinitor   
6.) CDK (cyclin-dependent kinase) 4 and CDK6: Ibrance

VEGF – stimulating angiogenesis as a key part of cancer growth. If a small tumor mass does not induce new blood vessel growth, it won’t grow bigger than 1mm in size. VEGF stimulates this. It is secreted by the cancer cells. It binds the VEGF receptor on vascular endothelial cells and stimulates those cells to grow. The Bevacizumab is an anti-body that binds to the VEGF and prevents it from binding the VEGF receptor.

Other target therapies might inhibit at the receptor level (HER2) using antibodies or small molecules; or at signal transduction (mTOR) using small molecules.

Immunotherapy: The use of medicines to stimulate a patient’s own immune system to recognize and destroy cancer cells more effectively.

Immune checkpoint inhibitors- keeps the immune system from attacking normal cells in the body. These checkpoints are molecules turned on or off to start an immune response (CTLA-4, PD-1). Cancer cells sometimes use these checkpoints to avoid being attacked by the immune system.

Tumor cells and other cells of the immune system keep the killer T cells “in check”: they do not recognize the cancer cells as not normal and don’t kill them.

The major advances in immunotherapy in the last 10 years has been the development of these checkpoint inhibitors that target PD-1, CTLA-4 on T cells that normally helps keep these cells from attacking other cells in the body. By blocking PD-1, these drugs boost the immune response against cancer cells. Nivolumab (Keytruda) for PD-1, Ipilimumab (CTLA-4).

* Types of Treatments for Individual Cancers

LUNG CANCER – most common cancer in men and women. 220k diagnosed per year. 1.5 million diagnosed worldwide.

Leading cause of cancer death around the world. Approx 160k deaths per 200k diagnoses. 1.3 million worldwide per 1.5 million worldwide. This is because most people present with metastatic cancer that is not amenable to radiation or surgery for cure. Because the cancer is metastatic at diagnosis, survival is generally measured in months to a few years.

Potential Lung Cancer treatments if localized: Surgery, remove the cancer and part of the lung.  
-Pneumonectomy: removal of a lung on one side.  
-Lobectomy: removal of a section or lobe.  
-Wedge resection: removal of part of a lobe.   
Radiation is used when surgery is not possible or if some cancer is left behind after surgery.

Treatment of metastatic disease in lung cancer: combination of chemotherapy and targeted therapy. Cisplatin + taxol or Carboplatin + Taxotere. Many regimens have been shown to have activity. Additionally, see patients treated with a doublette plus Avastin (VEGF), or doublette plus Tarceva (EGFR). There are a small percentage of NSCLC (~5%) that over express the gene ALK. If that’s the case, the doublette is also used with Xalkori (which targets the ALK mutation).

Immunotherapy was approved to treat metastatic lung cancer.

BREAST CANCER – Most common cancer in US women.  
230k cases diagnosed per year in the US. 40k deaths per year in the US.   
Second leading cause of cancer death.  
Survival measured in years for metastatic disease.

Treatment for localized breast cancer: Primary treatment is surgery with mastectomy or lumpectomy + radiation. (Surgeon removes the breast cancer lump, and then radiation is given to the rest of the breast to sterilize any microscopic disease.) These are considered equally curative for localized breast cancer.

For women at high risk of recurrence, a combination of drugs are used including:  
-Adriamycin, Taxol or Taxotere, 5-FU, Cytoxan, Carboplatin.  
-Targeted therapy can be added if HER2 positive, Herceptin

Treatment for metastatic breast cancer:  
-Many chemotherapy drugs are given in different combinations. Including the taxanes and the platinum agents.  
-Women also benefit from hormone therapy. Many breast cancers express estrogen receptor (ER+) and/or the progesterone receptor (PR+).

Hormone therapy to target ER is used in the adjuvant or metastatic settings to treat breast cancer (alone or in combination with chemotherapy).   
-Drugs that block estrogen binding: tamoxifen (most famous), fareston, faslodex.   
-Other newer agents include aromatase inhibitors that block estrogen production, including Femara and Arimidex, Aromasin.

Targeted Therapy for breast cancer includes drugs that block HER2, mTOR, as well as the cyclin kinases. (cell cyclin kinases)

PROSTATE CANCER

COLON CANCER

LIVER CANCER

STOMACH CANCER

* Clinical Trials