ONCOLOGY 101
What is Cancer?

- Cancer is a renegade system of growth that originates within a patient's biosystem, more commonly known as the human body. There are many different types of cancers, but all share one hallmark characteristic: unchecked growth that progresses toward limitless expansion.
- It is difficult to imagine anyone who has not heard of this illness. Most people have been affected because either they or their loved ones or friends are cancer survivors.
- Because cancer is so prevalent, people have many questions about its biology, detection, diagnosis, possible causes, and strategies for prevention.

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
CANCER

- Abnormal cell structure
- Uncontrolled growth
- Immortality
- Ability to spread
- Ability to invade other tissues
- Heightened sensitivity to intrinsic growth factors
- Accelerated use of nutrients
- Angiogenesis

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Different Kinds of Cancer

Some common carcinomas:
- Lung
- Breast (women)
- Colon
- Bladder

Leukemias:
- Bloodstream

Lymphomas:
- Lymph nodes

Some common sarcomas:
- Fat
- Bone
- Muscle

www.cancer.gov/cancertopics/understandingcancer/cancer
## Naming Cancers

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>adeno-</td>
<td>gland</td>
</tr>
<tr>
<td>chondro-</td>
<td>cartilage</td>
</tr>
<tr>
<td>erythro-</td>
<td>red blood cell</td>
</tr>
<tr>
<td>hemangio-</td>
<td>blood vessels</td>
</tr>
<tr>
<td>hepat-</td>
<td>liver</td>
</tr>
<tr>
<td>lipo-</td>
<td>fat</td>
</tr>
<tr>
<td>lympho-</td>
<td>lymphocyte</td>
</tr>
<tr>
<td>melano-</td>
<td>pigment cell</td>
</tr>
<tr>
<td>myelo-</td>
<td>bone marrow</td>
</tr>
<tr>
<td>myo-</td>
<td>muscle</td>
</tr>
<tr>
<td>osteo-</td>
<td>bone</td>
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www.cancer.gov/cancertopics/understandingcancer/cancer
Loss of Normal Growth Control

Normal cell division

Cell damage—no repair

Cell Suicide or Apoptosis

Cancer cell division

First mutation
Second mutation
Third mutation
Fourth or later mutation

Uncontrolled growth

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
The Beginning of Cancerous Growth

Underlying tissue
Tumors (Neoplasms)

Underlying tissue

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Invasion and Metastasis

1. Cancer cells invade surrounding tissues and blood vessels.

2. Cancer cells are transported by the circulatory system to distant sites.

3. Cancer cells reinvade and grow at new location.

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Malignant versus Benign Tumors

Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.

Time

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Malignant cells have 2 characteristics

- No clear cut borders—put their roots and grow into surrounding tissues.
  - Like weeds in the garden.
- May spread to other parts of the body
  - Called metastasis
  - If breast cancer metastasis to lungs considered breast cancer with metastasis to lung.
    - Patient does not have two cancers
Cancer a Group of Diseases

- There are specific methods of diagnosis, staging and treatment for each kind of cancer.
Diagnosis

- **Tests**
- **Biopsies**- determine the type and grade of disease.
  - Grade 1: well differentiated
  - Grade 2: Moderately differentiated
  - Grade 3: Poorly differentiated
  - Grade 4: Undifferentiated
- **Staging**- determining the extent of the disease
Biopsy

Patient’s tissue sample or blood sample

Pathology

Proteomic profile

Genomic profile

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
# Microscopic Appearance of Cancer Cells

<table>
<thead>
<tr>
<th>Normal</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Normal Cells" /></td>
<td><img src="https://via.placeholder.com/150" alt="Cancer Cells" /></td>
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</tbody>
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- **Large number of irregularly shaped dividing cells**
- **Large, variably shaped nuclei**
- **Small cytoplasmic volume relative to nuclei**
- **Variation in cell size and shape**
- **Loss of normal specialized cell features**
- **Disorganized arrangement of cells**
- **Poorly defined tumor boundary**
Carcinoma in Situ

- Norma
- Hyperplasia
- Mild dysplasia
- Carcinoma in situ (severe dysplasia)
- Cancer (invasive)

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Genes and Cancer

Chromosomes are DNA molecules

- Viruses
- Chemicals
- Radiation
- Heredity
DNA Structure

Chemical bases

DNA molecule

A
T
C
G
DNA Mutation

DNA

CAAGCTAACT

Normal gene

CAAGCAACT

Single base change

CAAGCCTAACT

Additions

CAAGAATCT

Deletions
Oncogenes

Normal cell

Normal genes regulate cell growth

Cancer cell

Oncogenes accelerate cell growth and division

Mutated/damaged oncogene
Proto-Oncogenes and Normal Cell Growth

Normal Growth-Control Pathway

Growth factor

Receptor

Signaling enzymes

DNA

Transcription factors

Cell nucleus

Cell proliferation
Oncogenes are Mutant Forms of Proto-Oncogenes

- Inactive growth factor receptor
- Inactive intracellular signaling protein
- Signaling protein from active oncogene
- Activated gene regulatory protein
- Transcription
- Cell proliferation driven by internal oncogene signaling
Tumor Suppressor Genes

Normal genes prevent cancer.

Remove or inactivate tumor suppressor genes.

Damage to both genes leads to cancer.

Cancer cell with mutated/inactivated tumor suppressor genes.

Normal cell with normal genes.

Tumor Suppressor Genes Act Like a Brake Pedal

Growth factor

Receptor

Signaling enzymes

Tumor Suppressor Gene Proteins

INHIBIT

INHIBIT

INHIBIT

DNA

Transcription factors

Cell nucleus

Cell proliferation

p53 Tumor Suppressor Protein Triggers Cell Suicide

Normal cell → Excessive DNA damage → Cell suicide (Apoptosis)

p53 protein
DNA Repair Genes

Normal DNA repair

Base pair mismatch

No DNA repair

No cancer

Cancer
Cancer Tends to Corrupt Surrounding Environment

Growth factors = proliferation

Invasive

Matrix

Fibroblasts, adipocytes

Proteases

Blood vessel

Cytokines, proteases = migration & invasion

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Tumor Staging

Five-Year Survival Rates for Patients with Melanoma (by stage)

- Stage I: 100%
- Stage II: 50%
- Stage III: 10%

Stage at Time of Initial Diagnosis

www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer
Goals of Therapy

- **Prevention**
  - Measures taken to avoid carcinogen exposure
- **Cure**
  - A complete response, no detectable disease
- **Control**
  - An extension of life when cure is unrealistic
- **Palliation**
  - Comfort when cure or control is impossible
  - Palliative cancer care is the integration of therapies that address the multiple issues that cause suffering.

Polovich, Olsen & LeFebvre, 2014
Treatment of Cancer

- Surgery
- Radiation
- Chemotherapy
- Biotherapy/Targeted agents
- Hormonal
Surgery: Intervention used for one or more of the following reasons.

- Establish a tissue diagnosis
- Determine the stage of disease
- Treat disease (removal all or a portion of the tumor)
  - Curative, Preventative or Palliative
- Place therapeutic and supportive hardware
- Assess treatment response
- Second-look surgery
- Reconstruction

Based on information from: Eggert, 2010; Polovich, Olsen & LeFebvre, 2014
Radiation

- Is a local treatment
- Use of high-energy rays to stop cancer cells from growing and multiplying
  - Affect all rapidly growing cells only in the area being treated with radiation
  - Normal cells that are injured during radiation are replaced by healthy cells after treatment is over
  - More effective for some diseases than others
- Dose of radiation is measured in rads
- Usually given once or twice daily over 4 to 6 weeks
- Can be given as radioimmunotherapy, combining radioisotope and a monoclonal antibody.
- Can be given in combination with chemotherapy

Based on information from: Eggert, 2010; Polovich, Olsen & LeFebvre, 2014
Types of Radiation

- **External Beam**
  - IMRT: Intensity-modulated radiation therapy
  - IGRT: Image-guided radiation therapy
  - Cyberknife: Allows for fast repositioning and delivery of tx from many different directions.

- **Internal Radiation Therapy:**
  - Brachytherapy: Sealed sources placed within or close to tumor

- **Radiopharmaceutical Therapy:**
  - Unsealed radioactive isotopes that are ingested, injected or instilled into a body cavity.

Eggert, 2010
Chemotherapy

- Systemic therapy rather than local therapy
- Use of drugs to destroy cancer cells
  - Different types kill at different stage of the cell’s life.
- Destroys fast growing cells (cancer & normal cells)
  - Limited by toxic effects on normal tissue
- Classified based on their mechanism of action, or where they exert their cytotoxic effect on the cancer cell.
- Traditionally given as Intravenous infusion, but can be given orally, subcutaneously, Intrathecal/intraventricular, intra-arterial, intraperitoneal, intra-pleural, Intra-vesicular and topically.

Based on information from: Eggert, 2010; Polovich, Olsen & LeFebvre, 2014
Treatment Approaches

- **Neo-adjuvant therapy:**
  - Therapy given before the primary therapy, usually means given before surgery.

- **Adjuvant therapy:**
  - Therapy given after the primary therapy, usually meaning after surgery.

- **Conditioning or preparative therapy**
  - May be with chemo or irradiation, to eliminate residual disease or empty the marrow space prior to receiving a stem cell transplant.

- **Immunosuppression**
  - Administration of chemotherapy at doses sufficient to blunt a patient’s immune response.

Polovich, Olsen & LeFebvre, 2014
Schedule

- Importance of Schedules
  - Treatment cycles are designated to permit recovery from damage to normal tissues and organs. Schedules are based upon these time frames.

- Protocol required tests
  - The study calendar in each protocol will indicate when testing needs to be done, and the schedule of therapy.

Polovich, Olsen & LeFebvre, 2014
Side Effects of Chemotherapy

- Different chemotherapy drugs give different side effects.
- Similar classes of chemotherapy drugs, may have similar side effects.
- In general, optimal treatment planning would try to avoid overlapping side effects, when more than one agent is given.
- Side effects on clinical trials need to be recorded in enough detail so that they can be graded utilizing the Common Toxicity Criteria grading scale.
Low Blood Counts

- **Myelosuppression:**
  - A significant decrease in the number of blood cells within the bone marrow

- **Low platelets:**
  - Thrombocytopenia (increased risk for bleeding)

- **Low Red Blood Cells**
  - Anemia (increased fatigue and Shortness of breath)

- **Low White Blood Cells, specifically the neutrophils**
  - Neutropenia (Increased risk for infection)
  - The most common dose-limiting toxicity
  - Can be life threatening

Polovich, Olsen & LeFebvre, 2014
Detecting Signs of Infection in Patients with Neutropenia

- **Neutropenia**: the often silent disorder
- **Only sign of an infection may be** **FEVER**:  
  - Fever is defined as a one-time oral temperature > 101° F (38.3 °C) lasting one hour  
  - When the ANC is <500/mcl or < 1,000/mcl (per NCCN guidelines)
- **Some common Sites of infection**  
  - GI tract  
  - Respiratory tract  
  - Genitourinary tract  
  - Indwelling devices  
  - Dermatologic and mucous membranes

Polovich, Olsen & LeFebvre, 2014
The ANC predicts the risk of infection

- Slight (<2,000)
- Minimal (<1,500)
- Moderate (<1,000)
- Severe (<500)

Grade 1
Grade 2
Grade 3
Grade 4

National Cancer Institute Grading System
Assessing the Neutrophils

The white blood count *(Lab values vary from institution to institution, check with your local lab for normal values)*

<table>
<thead>
<tr>
<th>White blood cells</th>
<th>3,500 – 11,000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Differential</strong></td>
<td></td>
</tr>
<tr>
<td>Neutrophil segs (or PMNs/polys)</td>
<td>59%</td>
</tr>
<tr>
<td>Neutrophil bands</td>
<td>3%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>30%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>5.3%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2.3%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
Assessing Neutrophils
The absolute neutrophil count

ANC = Total WBC x % of neutrophils (bands plus segs)

<table>
<thead>
<tr>
<th>Example</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• WBC</td>
<td>=</td>
<td>2,000/mm³</td>
</tr>
<tr>
<td>• Segmented neutrophils</td>
<td>=</td>
<td>55%</td>
</tr>
<tr>
<td>• Band neutrophils</td>
<td>=</td>
<td>1%</td>
</tr>
</tbody>
</table>

\[
ANC = 2,000 \times 0.56 = 1,120/mm³
\]
Absolute Neutrophil Count Calculation

WBC = 3,000/mm³

- Segmented neutrophils = 20%
- Band neutrophils = 5%
- Eosinophils = 3%
- Basophils = 1%
- Lymphocytes = 71%

What is the ANC?
Gastro-intestinal Side Effects

- **Nausea & vomiting**: Know the agent and its emetogenic potential to prevent
- **Diarrhea**: Loose or watery stools, record number of stools above baseline.
- **Constipation**: Excessive hard, dry bowel movements that are infrequent
- **Mucositis**: Inflammation of any mucosal membrane (Stomatitis refers to oral tissue inflammation)
- **Anorexia**: Loss of desire to eat
- **Cachexia**: Multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass

Polovich, Olsen & LeFebvre, 2014
Mouth Problems

- Dry mouth - Xerostomia
- Sore mouth: Stomatitis
- Dysgeusia: Altered taste
  - Platinum drugs can cause a metallic taste in mouth
- Dysphagia: Swallowing Difficulty
Hair

- Alopecia: hair loss
- Complete hair loss
  - May be gradual or sudden
  - Just the head or entire body
- Alopecia is a constant reminder of disease and greatly affects patient’s sense of self.
- Recommendation of hair prosthesis prior to treatment administration is recommended – may be covered by patient’s insurance

Polovich, Olsen & LeFebvre, 2014
Peripheral Neuropathy

- Numbness of Hands and or Feet
  - Can also be painful
- Occurs in 10 – 20% of patients
- Commonly associated with platinum drugs, taxanes, epothilones, vinca alkaloids, bortezomib and lenalidomide
- Caused by demyelination, which reduces nerve conduction velocity

Polovich, Olsen & LeFebvre, 2014
Urinary

- Red Urine
  - Some agents, such as doxorubicin can change the color of the urine to red

- Hemorrhagic cystitis
  - The inflammation of the mucosal surface of the bladders and/or ureters with the presence of sustained hematuria and lower urinary tract symptoms
  - A liver metabolite of cyclophosphamide and ifosfamide can bind to the bladder mucosa and cause this

Polovich, Olsen & LeFebvre, 2014
Pulmonary Toxicity

- **Dyspnea: Shortness of Breath**
- **Interstitial lung disease:**
  - Involves damage to the alveoli and surrounding interstitium
  - Bleomycin, ATRA, busulfan, carmustine, cyclophosphamide, ARA-C, gemcitabine, methotrexate, mitomycin, oxaliplatin,

- **Pulmonary Edema**
  - Related to cytokine induced capillary leak syndrome
  - Docetaxel is associated with fluid retention, alveolar permeability and pulmonary infiltrates

Polovich, Olsen & LeFebvre, 2014
Fatigue

- The most commonly reported symptom
- A distressing, persistent, subjective sense of physical, emotional, or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning.
- Tumor may be taking energy from body while competing for nutrients.

Some causes:
- Comorbid conditions
- Uncontrolled pain, nausea or vomiting
- Anxiety and stress
- Sleep disturbances
- Sleep disturbances
- Anemia
- Nutritional deficiencies
- Depression

Polovich, Olsen & LeFebvre, 2014
Biotherapy

- A treatment to boost or restore the ability of the immune system to fight cancer, infections and other diseases.
  - Includes mAbs, growth factors, and vaccines

- Methods of Action
  - Enhancing the patient’s own immune response
  - Altering the micro environment in which cancer cells grow
  - Increasing the vulnerability of cancer cells to the body’s own immune system
  - Altering the pathway by which normal cells transform into malignant cells
  - Prevent the metastasis of cancer cells
  - Enhancing the repair of normal cells damaged by treatment
  - Changing cancer cells so they behave like healthy cells

Polovich, Olsen & LeFebvre, 2014
Targeted Therapies in Cancer: Multiple Strategies, Multiple Targets

Targeting the Tumor Cell

- Alemtuzumab
- Trastuzumab
- Erb2 & Her2
- CD52
- CD20
- VEGF receptors
- Bevacizumab
- Vatalanib
- SU11248

- Gefitinib
- Imatinib mesylate
- RAS
- NUCLEUS
- PKC-alpha
- Isis 3521
- 26S proteasome
- Bortezomib
- Bcl2
- Oblimersen sodium
- Sorafenib

- Her1 receptor
- Her1 receptor
- Bcr-Abl

Endothelial cell
Categories of Biotherapy

- Cytokines: small protein molecules that provide communication between the cells of the immune system
  - Interferons
  - Interleukins
  - Growth Factors

- Monoclonal Antibodies (Mabs): Type of targeted therapy derived from human antibodies, mouse antibodies or a combination.
  - Cell surface proteins can function as targets for binding mABs
  - Target host tissues or proteins that support tumor growth
  - Potential for infusion reactions

Based on information from: http://www.cancer.gov/cancertopics/understandingcancer & Polovich, Olsen & LeFebvre, 2014
Categories of Biotherapy

- Small Molecules
  - Tyrosine kinase Inhibitors (ibs)
  - Targeted therapies are directed toward specific molecules along intracellular signaling pathway that is involved in tumor growth, proliferation and invasion.
- Oral agents (adherence issues)
- Vaccines
  - Goal of cancer vaccines is to harness the immune system to fight or destroy the tumor.

Based on information from: http://www.cancer.gov/cancertopics/understandingcancer & Polovich, Olsen & LeFebvre, 2014
Common Targets:

- **Tumor escape mechanism:**
  - Tumors can be targeted by the immune system through cell surface molecules.
  - Altered antigen expression on the tumor cell surface allows the antigen to go unrecognized by the immune system.

- **Angiogenesis**
  - The development of new blood vessels.
  - Tightly controlled in the normal cell.
  - In the malignant cell the balance is upset, leading to a cascade of irregular molecular and cellular events.
  - Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFBGF) induce angiogenesis.
  - Tumors release factors that elicit responses leading to neovascularization.

Polovich, Olsen & LeFebvre, 2014
Common Targets

- **Radio-immunotherapy:**
  - Radiolabeled, monoclonal antibodies.
  - Deliver radioactivity to tumor cells selectively.
  - Destroy or inactivate cancer cells while preserving the integrity of normal tissue.

- **Toxin-conjugated Molecules**
  - Physically attached to anti-tumor agents such as radioisotopes, chemotherapy drugs, toxins or other biologic agents.
  - Toxins such as diphtheria or pseudomonas are potent inhibitors of cell viability.
  - Antibodies and cytokines can be used to target these toxic molecules to cancer cells and depend upon the uptake to cause their death.
  - E.g. Gemtuzumab ozogamicin & denileukin diftitox

Polovich, Olsen & LeFebvre, 2014
Side Effects of Biologics

- Care is interdisciplinary
- Flu like symptoms
  - Fever/chills
  - Fatigue
  - Headache
- Anaphylaxis
- Dermatology: Rash, other dermatologic conditions, skin cancers
- Ophthalmology: Vision issues
- Gastroenterology: Development of polyps, colitis, diarrhea
- Endocrinology: Hypophysitis, diabetes, thyroid issues
Oncological Emergency

- Septic Shock
  - Temperature in neutropenia has a high mortality rate
- DIC
  - Bleeding
  - Leukemia
- SIADH (Water intoxication)
  - Confusion
  - Thirst, anorexia, nausea, fatigue, muscle cramps
  - Lung, Pancreas, Prostate, brain, HD
  - CTX, Vincristine, CDDP
  - Low Na+ levels
  - Restrict fluid, 3% NaCl
  - Slowly raise Na+ level, (cerebral edema)

- Tumor Lysis Syndrome
  - Massive & sudden release of cellular contents into the bloodstream.
  - Increase potassium, phosphorus and uric acid, and hypocalcaemia
  - Confusion
  - SCL, Leukemia, Lymphoma

- Hypercalcemia
  - Normal 9 – 11 mg/dL
  - Muscle weakness
  - Breast, Lung, Renal
  - Monitor Albumin

- Anaphylaxis
  - Increased sensitivity to drug

Polovich, Olsen & LeFebvre, 2014
Oncological Emergency

- Spinal Cord Compression 10 – 15% of pts
  - Back pain is usually the presenting symptom (70% Thoracic)
  - Numbness/constipation
  - Time is a factor
- Superior Vena Cava Syndrome
  - Swelling of face, eyelids, neck.
  - Obstruction of the Superior Vena Cava, preventing venous return to the heart from the head, neck, thorax and upper extremities.
- Cardiac Tamponade
  - Pressure on heart from too much fluid surrounding heart.
  - Complain of chest pain relieved when lean forward.

Polovich, Olsen & LeFebvre, 2014
The primary goal of any treatment is to improve survival and the quality of life!
References

