Why and what I need to know?

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Aims

- Learner be able to understand and review the basic approach to the diagnosis and treatment of cancer
- Discuss and comprehend the staging and how this affects the approach to treatment
- Evaluate the different approaches to cancer treatment and how decisions are made
Cancer Statistics

- 553,400 Americans died of cancer 2001
- 1.3 million new cases diagnosed
- 1 in 4 deaths from cancer
- Early detection/improvements in technology have improved prognosis for many

What do you think are the contributing factors to the incidence of cancer in the U.S. today?
Different Types of Cells

- Blood cells
- Muscle cells (smooth, striated, cardiac)
- Nerve cells
- Bone cells
- Cartilage cells
- Liver (hepa) cells

Above: Types of cell
Left: Nerve cells produced and grown in the laboratory from embryonic stem cells
### Main Features of Benign and Malignant Tumors

<table>
<thead>
<tr>
<th></th>
<th>Malignant Tumor</th>
<th>Benign Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of growth</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Nature of growth</td>
<td>Invades surrounding tissue</td>
<td>Expands in the same tissue</td>
</tr>
<tr>
<td>Spread</td>
<td>Metastasizes via the bloodstream and the lymphatic system</td>
<td>Does not spread</td>
</tr>
<tr>
<td>Cell differentiation</td>
<td>Usually poor</td>
<td>Nearly normal</td>
</tr>
</tbody>
</table>
CAUSES OF CANCER

- Radiation: 1%
- Occupational factors: 4%
- Alcohol: 3%
- Viruses: 7%
- Other: 10%
- Sunlight: 10%
- Tobacco: 30%
- Diet: 35%

5-10% Genes

Environment: 90-95%
There are four principal approaches to cancer control:

1. Prevention
2. Early Detection
3. Diagnosis and Treatment
4. Palliative Care
An Overview of Cancer

Variations in Rates

- Rates have large variations among populations
- 444.6 per 100,000 African Americans
- 402.1 per 100,000 Whites
- 272.4 per 100,000 Hispanics
- 279.3 per 100,000 Asian Pacific Islanders
- 152.8 per 100,000 Native Americans
Factors Believed to Contribute to Global Causes of Cancer

30% Smoking and alcohol use
(172,000 deaths due to smoking and 19,000 deaths due to alcohol use)

30–35% Unbalanced diet
(One-third of all cancer deaths due to too many high glycemic carbohydrates, too many calories leading to obesity, a lack of physical activity.)

18–20% Chronic infections
(Deaths occur mostly in poor countries due to hepatitis B virus, human papilloma virus, HIV, human T-cell leukemia/lymphoma, and others.)

18–20% Hormones

2% Occupation
(Deaths occur mostly where pollution is heavy.)

1% Pollution
<table>
<thead>
<tr>
<th>Type</th>
<th>Decreases Risk</th>
<th>Increases Risk</th>
<th>Preventable by Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Vegetables, fruits</td>
<td>Smoking; some occupations</td>
<td>33–50%</td>
</tr>
<tr>
<td>Stomach</td>
<td>Vegetables, fruits; food refrigeration</td>
<td>Salt; salted foods</td>
<td>66–75%</td>
</tr>
<tr>
<td>Breast</td>
<td>Vegetables, fruits</td>
<td>Obesity; alcohol</td>
<td>33–50%</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>Vegetables; physical activity</td>
<td>Meat; alcohol; smoking</td>
<td>66–75%</td>
</tr>
<tr>
<td>Mouth/throat</td>
<td>Vegetables, fruits; physical activity</td>
<td>Salted fish; alcohol; smoking</td>
<td>33–50%</td>
</tr>
<tr>
<td>Liver</td>
<td>Vegetables</td>
<td>Alcohol; contaminated food</td>
<td>33–66%</td>
</tr>
<tr>
<td>Cervix</td>
<td>Vegetables, fruits</td>
<td>Smoking</td>
<td>10–20%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Vegetables, fruits</td>
<td>Deficient diet; smoking; alcohol</td>
<td>50–75%</td>
</tr>
<tr>
<td>Prostate</td>
<td>Vegetables</td>
<td>Meat or meat fat; dairy fat</td>
<td>10–20%</td>
</tr>
<tr>
<td>Bladder</td>
<td>Vegetables, fruits</td>
<td>Smoking; coffee</td>
<td>10–20%</td>
</tr>
</tbody>
</table>

Here are some tips issued by a panel of cancer researchers:

- Avoid being underweight or overweight, and limit weight gain during adulthood to less than 11 pounds.
- If you don’t get much exercise at work, take a 1-hour brisk walk or similar exercise daily, and exercise vigorously for at least 1 hour a week.
- Eat 8 or more servings a day of cereals and grains (such as rice, corn, breads, and pasta), legumes (such as peas), roots (such as beets, radishes, and carrots), tubers (such as potatoes), and plantains (including bananas).
- Eat 5 or more servings a day of a variety of other vegetables and fruits.
- Limit consumption of refined sugar.
- Limit alcoholic drinks to less than 2 a day for men and 1 for women.
- Limit intake of red meat to less than 3 ounces a day, if eaten at all.
- Limit consumption of salted foods and use of cooking and table salt. Use herbs and spices to season foods.

Sources: World Cancer Research Fund, American Institute for Cancer Research.
Hallmarks of Cancer
Target Areas for Therapeutic Interventions

- Aneuploidy
- Angiogenesis
- Altered Energy Metabolism
- Invasivity
- Motility
- Immune Defense Evasion
- Immortalization (Anti-Apoptosis)
- Deregulated Proliferation
Diagnosis

- Biopsy
- Surgery
- Complex cases

monitoring
# Cancer’s Seven Warning Signals

1. Changes in bowel or bladder habits
2. A sore that does not heal
3. Unusual bleeding or discharge
4. Thickening or lump in breast or elsewhere
5. Indigestion or difficulty in swallowing
6. Obvious change in a wart or mole
7. Nagging cough or hoarseness

If you have a warning signal, see your doctor.
How to Examine Your Breasts

Do you know that 95% of breast cancers are discovered first by women themselves? And that the earlier the breast cancer is detected, the better the chance for a complete cure? Of course, most lumps or changes are not cancer. But you can safeguard your health by making a habit of examining your breasts once a month—a day or two after your period, or, if you’re no longer menstruating, on any given day. And, if you notice anything changed or unusual—a lump, thickening, or discharge—contact your doctor right away.

How to Feel for Changes

Step 1
Lie down and put a pillow or folded bath towel under your left shoulder. Then place your left hand under your head. (From now on you will be feeling for a lump or thickening in your breasts.)

Step 2
Imagine that your breast is divided into quarters.

Step 3
With the fingers of your right hand held together, press firmly but gently, using small circular motions to feel the inner, upper quarter of your left breast. Start at your breastbone and work toward the nipple. Also examine the area around the nipple. Now do the same for the lower, inner portion of your breast.

Step 4
Next, bring your arm to your side and feel under your left armpit for swelling.

Step 5
With your arm still down, feel the upper, outer part of your breast, starting with your nipple and working outward. Examine the lower, outer quarter in the same way.

Step 6
Now place the pillow under your right shoulder and repeat all the steps, using your left hand to examine your right breast.

How to Look for Changes

Step 1
Sit or stand in front of a mirror with your arms at your side. Turning slowly from side to side, check your breasts for:
- changes in size or shape
- puckering or dimpling of the skin
- changes in size or position of one nipple compared to the other

Step 2
Raise your arms above your head and repeat the examination in Step 1.

Step 3
Gently press each nipple with your fingertips to see if there is any discharge.
Stage I local
Stage II local
Stage III locally advanced
Stage IV metastasis
STAGES OF CANCER (COLON)

Stage 0: Very early cancer on the innermost layer of the intestine

Stage I: Cancer is in the inner layers of the colon

Stage II: Cancer has spread through the muscle wall of the colon

Stage III: Cancer has spread to the lymph nodes

Stage IV: Cancer that has spread to other organs
Paul Ehrlich 1854 - 1915

- Father of Chemotherapy
- Salvarsan for Treatment of Syphilis
- Nobel Prize 1908
- "Magic Bullet Concept"
Multidisciplinary approach

- Team
- Surgeon
- Oncologist
- Radiation oncologist
- Physical Medicine
- Cardiologist
- Social worker
- Psychiatrist
- Gastroenterologist
- Cancer geneticist
- Nurse
- Pharmacist
MODALITIES OF TREATMENT

1-local therapy:
- surgery.
- radiation therapy.

2-systemic treatment:
- chemotherapy.
- Hormonal therapy.
- Monoclonal antibodies.
- Radioactive material.

3-supportive care.

4-non-conventional therapy.
Timeline history of chemotherapy development

1908 - Discovery of Arsenphenamine

1928 - Alexander Fleming - Penicillin

190 - Paul Ehrlich - Father of Chemotherapy

1939 - Gerhard Domagk - Sulfonamidochrysoidine (Prontosil)

1942 - Prontosil - First sulfonamide - Bayer's Laboratory

1943 - Nitrogen mustard in lymphomas

1948 - Anifolates

1951 - Thiopurines

1957 - 5-Fluorouracil

1958 - Methotrexate

1959 - Antitumor antibiotics

1962 - Nalidixic acid

1963 - Vinca alkaloids

1963 to 1970 - Treatment for Hodgkin's disease

1996 - Imatinib

1997 - Monoclonal antibody approved for the treatment of tumor.

2005 - Tyrosine kinase inhibitors

2007 - Target specific screens
Cancer and the Immune System

For years, scientists have questioned why the immune system does not aggressively fight off cancer cells. New evidence suggests that T-cells, which are crucial to the body's immune response, have a protein (CTLA-4) that actually suppresses their ability to attack cancer cells. Researchers are focusing on that protein in hopes of creating a more aggressive immune system that could kill cancer cells.

**HOW T-CELLS DETECT ENEMY CELLS**

For T-cells to be turned on, they must receive **two signals** that tell them to attack a foreign cell.

**PROBLEM 1**

Tumor cells do not have B7 molecules needed to turn T-cells on.

**SIGNAL 1:** A receptor on the T-cell must recognize the cancer cell's antigen, which identifies the cell as being foreign.

**SIGNAL 2:** B7 molecules on the enemy cell must be detected by the CD28 protein on the T-cell.

**MISSING SIGNAL**

ANTIGEN

RECEPTOR

CD28 PROTEIN

T-CELL

DOESN'T ATTACK CANCER CELL

**PROBLEM 2**

Molecules of the antigens bind to the CTLA-4 protein on the T-cell, sending a signal to turn the T-cell off.

**TURNING T-CELLS ON**

Dendritic cells, part of the immune system, break up the cancer's antigen and present it to the T-cell to provoke a response. But they also have the ability to turn the T-cell off.

**DENDRITIC CELL**

B7 MOLECULE

CTLA-4 PROTEIN

T-CELL

DOESN'T ATTACK CANCER CELL

**ONE POSSIBLE SOLUTION**

Scientists have shown that injecting antibodies to CTLA-4 prevented the protein from binding with molecules on the T-cell and sending the third signal.

**SOLUTION**

Antibodies to the CTLA-4 on the T-cell bind to the protein, blocking the signal and keeping the T-cell on.

ANTIBODIES

ATTACKS CANCER CELL

Source: Dr. James P. Allison, Memorial Sloan-Kettering Cancer Center
B. Mechanism of action

- cell membrane
- metabolism
- Cell wall synthesis
- m-RNA code
- Ribosomes
- DNA gyrase
- THFA
- PABA
- protein synthesis
MODES OF CHEMOTHERAPY

- PRIMARY CHEMOTHERAPY - chemotherapy is used as the sole anti-cancer treatment in a highly sensitive tumor types
  - Example – CHOP for Non-Hodgkins lymphoma

- ADJUVANT CHEMOTHERAPY - treatment is given after surgery to “mop up” microscopic residual disease
  - Example – Adriamycin, cyclophosphamide for breast cancer

- NEOADJUVANT CHEMOTHERAPY - treatment is given before surgery to shrink tumor and increase chance of successful resection
  - Example – Adriamycin, ifosfamide for osteosarcoma
CONCURRENT CHEMOTHERAPY - treatment is given simultaneous to radiation to increase sensitivity of cancer cells to radiation

Example – Cisplatin, 5-fluourouracil, XRT for head and neck tumors
GOMPertzian Growth

Growth rates are exponential at early stages of development and slower at later stages of development.

Biological growth follows this characteristic curve.
AIM OF COMBINATION CHEMOTHERAPY

INCREASED EFFICACY

ACTIVITY

Different mechanisms of action
Different mechanisms of resistance

SAFETY

Compatible side effects
## Combination chemotherapy: Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Agents</th>
<th>Dose Intensity</th>
<th>PR (%)*</th>
<th>CR (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>1</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>1</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Doxorubicin (A)</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>CMF</td>
<td>0.5+0.33+0.33</td>
<td>1.17</td>
<td>50</td>
</tr>
<tr>
<td>CAF</td>
<td>0.5+0.7+0.33</td>
<td>1.53</td>
<td>75</td>
</tr>
</tbody>
</table>

* Patients with overt metastases and no prior chemotherapy except in the adjuvant setting

PR = partial response
CR = complete response

S: Replication of DNA

G1: Gap 1 (Cell Grows)

G2: Gap 2 (Cell Prepares to Divide)

M: Mitosis (Cell Division)

Cells that Cease Division

Cell cycle cartoon image is courtesy of The Science Creative Quarterly (www.scq.ubc.ca), Jane Wang, Illustrator.
HEMATOLOGICAL CONSIDERATIONS FOR DOSE SCHEDULING

- Lifespan
  - Platelet - 7-10 days
  - Red blood cell - 120 days
  - Neutrophils - 6-12 hours

- Time from Stem Cell to Mature Neutrophil
  - ~7-10 days
SIDE EFFECTS OF CHEMOTHERAPY

- Mucositis
- Alopecia
- Pulmonary fibrosis
- Cardiotoxicity
- Local reaction
- Renal failure
- Myelosuppression
- Phlebitis
- Nausea/vomiting
- Diarrhea
- Cystitis
- Sterility
- Myalgia
- Neuropathy
CRITERIA USED TO DESCRIBE RESPONSE ARE:

- **Complete response** (complete remission) is the disappearance of all detectable malignant disease.
- **Partial response**: is decrease by more than 50% in the sum of the products of the perpendicular diameters of all measurable lesions.
- **Stable disease**: no increase in size of any lesion nor the appearance of any new lesions.
- **Progressive disease**: means an increase by at least 25% in the sum of the products of the perpendicular diameters of measurable lesion or the appearance of new lesions.
TARGETED THERAPIES

- **Monoclonal antibodies**: proteins that trigger the body’s pathways involved in cancer growth to fight cancer more effectively.

- **EGFR**: family of receptors found on surface of normal and cancer cells that bind with an epidermal growth factor (EGF) causing cells to divide.

- **Tyrosine Kinase Inhibitors**: Part of the cell that signals it to divide and multiply; enhances cell growth. Still investigational.
Tumor Cell Stimulation

Gene Transcription
- Cell Cycle Progression
- Angiogenesis
- Survival
- Proliferation
- Metastases
- Antiapoptosis
Prevention is better than cure!!

Good Habits

Bad Habits
Thank you

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