Antineoplastic Agents: Cancer Treatment

• One out of every three people will develop some form of cancer in their lifetime.
• The five-year survival rate for these patients has steadily risen over the past half-century to nearly 50%.
  ▪ Early Diagnosis
  ▪ Therapy
  ▪ Prevention

Cancer’s Seven Warning Signs

C hange in bowel or bladder habits
A sore that does not heal
U nonsual bleeding or discharge
T hickening or lump in breast or elsewhere
I ndigestion or difficulty in swallowing
O bvious change in wart or mole
N agging cough or hoarseness

Source: American Cancer Society
### Antineoplastic Agents: Statistics

#### ESTIMATED NEW CASES AND DEATHS FOR MAJOR SITES OF CANCER - 2010

<table>
<thead>
<tr>
<th>Site or type</th>
<th>Number of cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>240,330</td>
<td>139,580</td>
</tr>
<tr>
<td>Colon-rectum</td>
<td>142,570</td>
<td>51,370</td>
</tr>
<tr>
<td>Breast</td>
<td>209,060</td>
<td>40,230</td>
</tr>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>32,050</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>131,260</td>
<td>28,580</td>
</tr>
<tr>
<td>Bladder</td>
<td>43,470†</td>
<td>7,950</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>74,930†</td>
<td>21,530</td>
</tr>
<tr>
<td>Oral</td>
<td>36,540</td>
<td>7,880</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,140</td>
<td>36,800</td>
</tr>
<tr>
<td>Leukemia</td>
<td>43,050†</td>
<td>21,840</td>
</tr>
<tr>
<td>Melanoma</td>
<td>68,130†</td>
<td>8,700</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,000</td>
<td>10,570</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,880</td>
<td>13,850</td>
</tr>
<tr>
<td>All sites‡</td>
<td>1,529,880</td>
<td>969,490</td>
</tr>
</tbody>
</table>

* Includes cervix. If carcinoma in situ is included, cases total over 60,000.
† Estimated new cases of skin cancer (non-melanoma) = about 300,000.
‡ Includes additional sites.

**NOTE:** Estimates are based on rates from the NCI SEER program 2010.
Antineoplastic Agents: Cancer Treatment

- Cancer cells are formed when normal cells lose the normal regulatory mechanisms that control growth and multiplication.
- In general, the abnormal growth of the cells is caused by disregulation in the cell cycle by abnormal cell signaling.
Antineoplastic Agents: Cellular Kinetics

Schematic Representation of the Life Cycle of a Human Tumor

Antineoplastic Agents: Causes of Cancer

Most cancers arise from chance events involving changes in cellular DNA.

- Collateral damage to DNA caused by reactive chemicals.
- Damage caused by the cells and products of the immune system.
- Ultraviolet or other radiation.
- Abnormal products of diseased cells.
Antineoplastic Agents: Definitions

- **Blastoma**: a new growth or malignant tumor of immature, undifferentiated cells.
- **Carcinoma**: a new growth or malignant tumor that occurs in epithelial tissue. Usually infiltrate and give rise to metastases.
- **Fungoides**: cell mass presenting itself such that it looks like a fungus.
- **Lymphoma**: growth in lymph system.
- **Sarcoma**: cancer arising from connective tissue such as muscle or bone.

Antineoplastic Agents: Chemotherapy History

Devitia, V.T.; Chu, E. Cancer Res. 2008, 68, 8643-8653
**Antineoplastic Agents: Chemotherapy History**

Devilia, V.T.; Chu, E. Cancer Res. 2008, 68, 8643-8653

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**Antineoplastic Agents: Chemotherapy Targets**

- Purine Synthesis
- Pyrimidine Synthesis
- Ribonucleotides
- Deoxyribonucleotides
- Topo II
- DNA
- RNA
- Proteins
Chemotherapeutic Agents: Classification

- Alkylating Agents
- Antimetabolites
- Natural Products
- Miscellaneous Agents
Chemotherapeutic Agents: Alkylating Agents

Mechlorethamine

Cyclophosphamide

Melphalan

Chlorambucil

Chemotherapeutic Agents: Alkylating Agents

R-N-Cl Cl

Cl- R-N-Cl

Cl- R-N-Cl Nu1

R-N-Cl Nu1 Nu2

R-N-Cl Nu1 Nu2 connected
Chemotherapeutic Agents: Alkylating Agents

Chemotherapeutic Agents: Alkylating Agents

DNA Chain Scission

depurinated DNA chain +
depurination

DNA

ring cleavage

abnormal base pair with thymine

cross-linking with second guanine
Chemotherapeutic Agents: Alkylating Agents
Chemotherapeutic Agents: Alkylating Agents

Chemotherapeutic Agents: Alkylating Agents
**Chemotherapeutic Agents: Alkylating Agents**

- Cyclophosphamide was designed to act as a prodrug for a nitrogen mustard.
- Cancer cells have high phosphatase activity (related to tyrosine kinases and their intimate relation to cellular signaling).

![Chemotherapeutic Agents: Alkylating Agents](image-url)
Chemotherapeutic Agents: Alkylating Agents

- Triethylenemelamine
- Busulfan

Chemotherapeutic Agents: Antimetabolites

- Drugs that are chemically similar to naturally occurring metabolites, but differ enough to interfere with normal metabolic pathways.
  - Folic acid analogs
  - Pyrimidine analogs
  - Purine analogs
Chemotherapeutic Agents: Antimetabolites

pteroylglutamic acid (folic acid)

methotrexate (MTX)

Chemotherapeutic Agents: Antimetabolites

cytarabine (cytosine arabinoside)

fluorouracil
Chemotherapeutic Agents: Antimetabolites

6-Mercaptopurine

Adenosine

Pentostatin (deoxycoformycin)

Chemotherapeutic Agents: Natural Products

R = CH₃  Vinblastine
R = CHO  Vincristine

Taxol
Chemotherapeutic Agents: Natural Products

Etoposide $R = \text{CH}_3$

Teniposide $R = \text{[thiophene group]}$
Chemotherapeutic Agents: Natural Products

dactinomycin

Chemotherapeutic Agents: Natural Products

O$_2$ $\rightarrow$ $O_2^+$
Chemotherapeutic Agents: Misc. Agents

Cisplatin

Transplatin

Chemotherapeutic Agents: Misc. Agents

Hematoprphyrin

a Porphyrin

Phthalocyanine derivatives
Second Generation Photosensitizers

Metatetrahydroxyphenylchlorin (a Chlorin)
Chemotherapeutic Agents: Misc. Agents