Principles of Cancer Therapy

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Learning Objectives:

By the end of this lecture, you will be able to:

1) List modalities for cancer therapy.
2) Describe principles of chemotherapy.
3) List factors affecting response to radiotherapy.
4) List complications of radiotherapy.
There are many modalities:

1- Surgical treatment.
2- Chemotherapy.
3- Radiotherapy.
4- Hormonal therapy.
Cellular biology:

Two phases in cell cycle:

1) Mitosis (cell division).

2) Interphase which consists of:

   a. G1 phase: variable duration, diploid content of DNA.

   b. S phase: DNA is duplicated.

Growth fraction of tumor:

The proportion of actively dividing cells, the higher the growth fraction, the faster is the doubling time of the tumor.

Chemotherapeutic agents and radiation kill cells by first order kinetics which means that a constant proportion of cells is killed for a given dosage.

Both chemotherapy and radiotherapy are active against actively dividing cells, i.e. growth fraction.
Chemotherapy:  

Classification according to the mode of action relative to the cell cycle:

a. Cell cycle non-specific agents e.g. alkylating agents, cisplatinum.
b. Cell cycle specific agents e.g. methotrexate on S phase, bleomycin on G2 phase.
**Principles of chemotherapy:**

1) Drugs are selected in particular tumor on the basis of previous experience with that tumor.

2) The drugs are usually given systematically. In order to increase their concentration locally, they may be administered by intrathecal or intracavitary.

3) Generally not administered if WBC count is less than 3000 cell/ml³ or platelet count is less than 100,000, because this means severe bone marrow suppression.

4) Blood count is obtained 7-14 days after treatment, and subsequent doses may need to be reduced depending on the degree of myelosuppression.

5) Dosage reduction may be taken due to toxicity of other organs like liver, kidneys.
6) Resistance to chemotherapy may be temporary due to devascularization or could be permanent due to undergoing mutation.

**Examples:**

A. Alkylating agents: has the ability to cause alkylation to DNA, resulting in cross linkage between DNA strands thus prevention of DNA replication such as cyclophosphamide.

B. Antimetabolites: they produce metabolic block because they closely resemble normal intermediaries for which may substitute in biochemical reaction e.g. methotrexate.

C. Antibiotics: they are naturally occurring elaborated by certain species of streptomyces, they inhibit both DNA and RNA synthesis e.g. bleomycin.
D. Plant alkaloids: they interfere with cellular microtubules and cause metaphase arrest e.g. Vincristine.

E. Other drugs: cisplatin is important in gynecology, cause inhibition of DNA synthesis by forming interstrand and intrastrand linkages.

Complications of chemotherapy:

1. Acting on the rapidly dividing cells of normal tissues causing gastritis, nausea and vomiting, stomatitis. On bone marrow causing cytopenia. On hair follicles, causing hair loss.

2. Specific side effects of the drugs.
Radiotherapy:

Radiation may be defined as the propagation of energy through space of matter.

Types of radiation includes electromagnetic and particulate.

Example of electromagnetic radiation includes infra-red, ultraviolet, x-ray, gamma ray.

Particulate radiation: consists of the kinetic energy of the moving particles examples neutrons (no charge), protons (positive charge), electrons (negative charge).

Unit of radiation measurement: the gray (Gy) is equivalent to an absorbed energy of one joule/kg of absorbing material.
**Biological considerations:**

1. **Ionization of the molecules:** radiation damage is caused by ionization of the molecules in the cells with production of free radicals that kill the tumor cells.

2. **Oxygen effect:** in the absence of oxygen, cells show a 2-3 fold increase in their capacity to survive radiation exposure, this means that hypoxic cells are less radiosensitive. This oxygen effect has important clinical applications:

   a. Anemic patients should have blood transfusion before undergoing radiotherapy.

   b. Bulky tumors are usually poorly vascularized and therefore often hypoxic, particularly the center, therefore such areas can be radioresistant.
3. Pharmacologic modification of the effect of radiation: this application has demonstrated significant survival advantage, particularly in local disease control e.g. when cisplatin – containing chemotherapy is given concurrently with radiation for locoregionally advanced Ca cervix.

4. Time-dose fractionation of radiation: the total dose is given in multiple fractions. Successful radiation therapy requires a delicate balance between dosage to the tumor and that to the surrounding normal tissue. Cells that survive the acute effect of radiation usually repair sublethal damage within 24 hours.
Major factors influencing the outcome of radiation therapy:

1) Normal tissue tolerance.
2) Malignant cell type.
3) Total volume irradiated.
4) Total duration of therapy.
5) Total dose delivered.
6) Number of fractions.
7) Type of equipment.
8) Tissue oxygen concentration.
Modalities of radiation therapy:

There are two techniques; teletherapy and brachytherapy. In teletherapy, the device is away from the patient as in external beam technique.

In brachytherapy, the radiation source is placed either within or close to the target tissue as in intracavitary and interstitial technique.
A) External radiation: allows a uniform dose to be delivered to a given field. It is usually used to shrink a large tumor mass before brachytherapy.

B) Intracavitary radiation: used particularly in treatment of cervical and vaginal cancer.

C) Interstitial radiation: the radioactive source is placed directly in the tumor and may be delivered by removable or permanent implants.

Permanent implants are used for inaccessible tumors, radioisotopes such as radon$^{222}$, or iodine$^{125}$ are used. Removable implants are placed in tumors that are accessible such as cervical or vaginal tumors.
Complications associated with radiation:

1. Acute complications:
   a. Acute cystitis: urgency, frequency, hematuria.
   b. Acute proctosigmoiditis, enteritis.
   c. Bone marrow suppression.

2. Chronic complications:
   a. Radiation enteropathy.
   b. Vaginal vault necrosis.
   c. Urological injuries.
   d. Fibrosis.
   e. Endarteritis: thickening and obliteration of small blood vessels.
Hormonal therapy:

Estrogen and progesterone receptor status of endometrial and breast cancer have prognostic and therapeutic significance. The hormones bind in the cytoplasm with receptors then there is translocation of the receptor hormone complex to the nucleus and then transcription of DNA. Estrogen exposure increase the production of both estrogen receptor and progesterone receptor while progesterone inhibits them. Hormonal therapy is used for recurrent or metastatic Ca endometrium and Ca breast.
**Pain management:**

Pain results from soft tissue inflammation, bone involvement, neural involvement, muscle spasm, infection and bowel colic.

Drugs used include:

1. Acetaminophen

2. Opioids for severe pain, controlled release morphine tablets are a significant advance.

3. When pain is neurogenic, an opioid and a peripherally acting drug should usually be supplemented by a tricyclic antidepressant, anticonvulsant or corticosteroid.
Care of terminally ill patients:

1. Symptoms control: as pain, nausea and vomiting.
2. Psychological support of the patient and her family.
3. Supportive measures as diet, physiotherapy.
4. In certain centers there are institutes for such patients with special trained nursing staff.
Thank You