MATHURADAS MOHOTA COLLEGE OF SCIENCE, NAGPUR

Seminar topic
on

"Radiation Sensitizers And Protectors ."

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Introduction

- Radiotherapy is regarded as one of the most important therapeutic modality for the treatment of malignant lesions.

- This field is undergoing rapid advancements in the recent times.

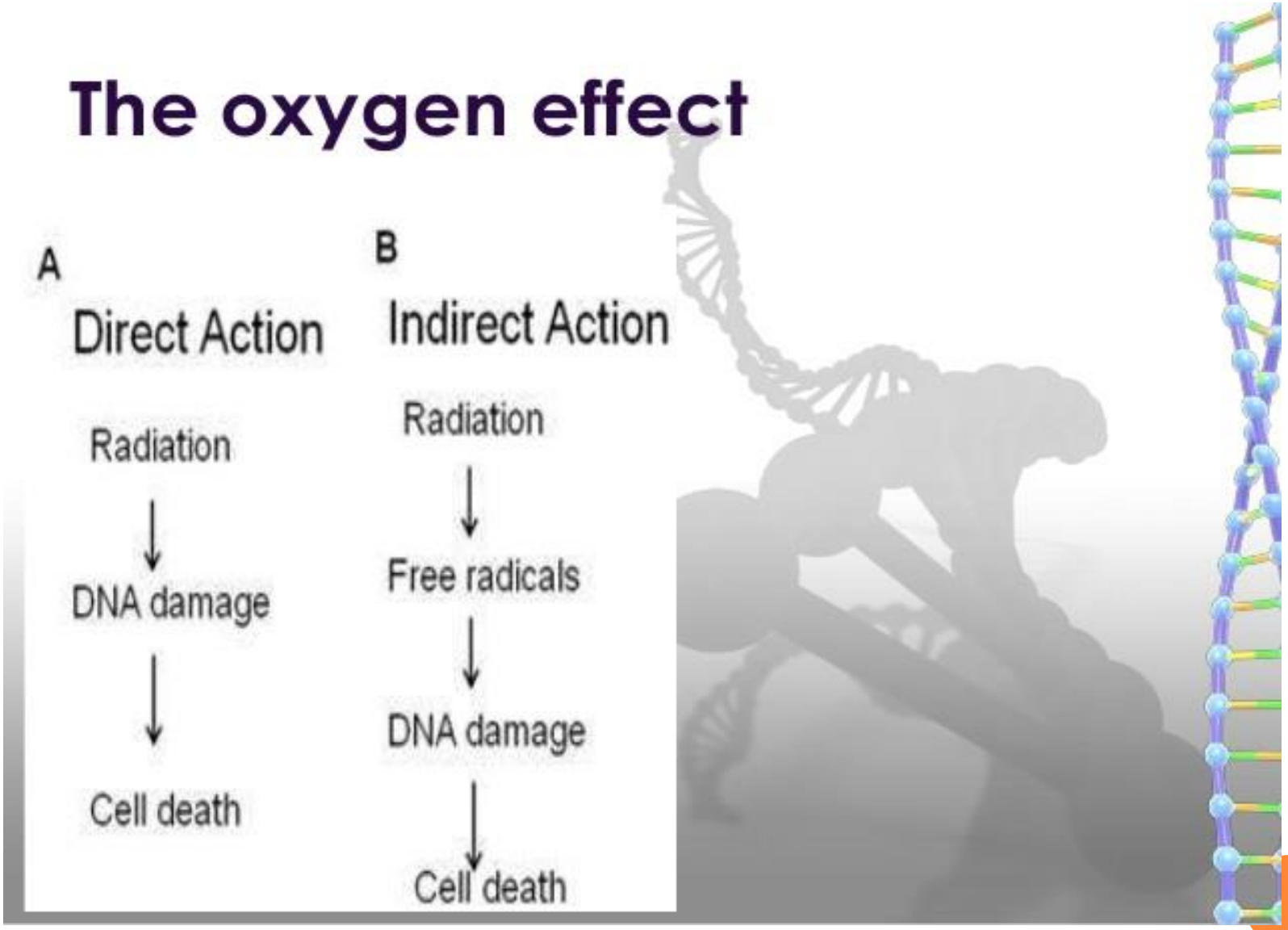
- The use of radiosensitizers and radioprotective agents, the course of radiotherapy has improved the sensitization of tumor cells and protection of normal cells, respectively.

- Every agent has its own application, mode of action, and adverse effects. In majority of instances, the success rate of radiotherapy is related to radiosensitizers and the patient's quality of life is dependent on the radioprotectors.

Mechanism of action

- Radiation therapy works by damaging the DNA of cancerous cells. This DNA damage is caused by energy changes, photon or charged particle. This damage is either direct or indirect ionization of the atoms which make up DNA chain. Indirect ionization happens as a result of the ionization of water, forming free radicals, notably hydroxyl radicals, which then damage the DNA.

The oxygen effect



Radiosensitizer

- These are the agents that sensitize the tumor cells to radiation.

VARIOUS TYPES OF RADIOSENSITIZERS

- Hyperbaric oxygen
- Carbogen
- Nicotinamide
- Metronidazole and its analogs
- Hypoxic cell cytotoxic agents
- Membrane active agents
- Radiosensitizing nucleosides
- Novel radiosensitizers

HYPERBARIC OXYGEN

- Oxygen is known to increase the radiosensitivity of cells.

- The reactions of oxygen with aqueous as well as organic-free radicals induced by ionizing radiations may lead to the production of very toxic and relatively stable peroxy radicals and hydrogen peroxide resulting in the damage to biomolecules and structures.

- Therefore, the simplest approach to enhance the radiosensitivity of hypoxic tumor cells would be to increase the oxygen tension in the tumor.

CARBOGEN

- The notion of improving tumor oxygenation by breathing highly oxygenated air has been revived recently by experiments in which subjects breathe carbogen, a mixture of 95% oxygen and 5% carbon dioxide that does not produce vasoconstriction associated with breathing 100% oxygen.

METRONIDAZOLE AND ITS ANALOGS

- Metronidazole and its analogues such as misonidazole, etanidazole, and nimorazole are used as radiosensitizers.

- Misonidazole has been observed to deplete sulfydral groups in cells, inhibit glycolysis and the repair of radiation indused cellular potentially lethal damage.

- They have been found to be effective in sensitizing hypoxic tumor cells.

- They fix the radiation damage by preventing the chemical restitution of free radicals.

HYPOXIC CELL CYTOTOXIC AGENTS

- Hypoxic cell cytotoxic agents include Mitomycin-C and Tirapazamine. Both are the bioreductive alkylating agent.

- In Lung, head and neck cancer have shown positive results.

MEMBRANE ACTIVE DRUGS

- Cell membranes, besides DNA, could also be critical targets for cell killing.

- These drugs were observed to increase the radiosensitivity of bacterial cells under hypoxic condition.

- Inhibition of the rejoining of radiation induced DNA strands breaks by chlorpromazine has been observed in mammalian and human cancer cells.

RADIOSENSITIZING NUCLEOSIDES

1. **Fluropyrimidines**: 5-Fluorouracil (FUra) and Fluorodeoxyuridine (FdUrd) are analogues of uracil and deoxyuridine, respectively.

2. **Thymidine Analogs** : bromodeoxyuridine (BrdUrd) and iododeoxyuridine (IdUrd) have been used as radiosensitizers.

3. **Gemcitabine** : Gemcitabine is an analog of deoxycytidine that has demonstrated effectiveness as a single agent against solid tumors.

4. **Fludarabine** : Fludarabine is a well-studied DNA damage repair inhibitor.

NOVEL RADIOSENSITIZERS

Taxanes

- This group of anticancer agents have a novel mechanism of action, broad clinical activity, and potential as clinical radiosensitizers.

- Paclitaxel and Docetaxel are the agents of this group.

Irinotecan

- It is a camptothecin derivative that is thought to exert its cytotoxic effects by targeting topoisomerase I.

Mechanism of radiosesitizer

- 1) **Non Hypoxic Cell Sensitizers**

  Differential effect is based on the premise that tumor cell cycle is faster and therefore incorporate more drug than the surrounding normal tissue. Ex. Halogenated Pyramidines

- 2) **Hypoxic Cell Sensitizers**

  Increase the radiosensitivity of cells deficient in molecular Oxygen (tumor cells) but have no effect on normally aerated cells.

Radioprotectors

- These are the compounds that are designed to reduce the damage in normal tissues caused by radiation.

- Radioprotective agent are useful in eliminating or reducing the severity of deleterious cellular effects which are caused by exposure to internal and or external irradiation in patients.

LIST OF RADIOPROTECTORS

- Amifostine
- Nitroxides
- Other anti-oxidants
- Cysteine and Cysteamine
- Melatonin
- Novel radioprotectors

AMIFOSTINE

- Amifostine (WR-2721) is one of today's most widely studied protectors.
- Amifostine selectively protects a broad range of normal tissues, including the oral mucosa, salivary glands, lungs, bone marrow, heart, intestines, and kidneys.
- Amifostine on administration undergoes metabolism and gets converted into WR-1065, which can readily permeate the cell membrane.

Other antioxidants

- Multiple vitamin antioxidants have been tested as a method to reduce the toxicity of radiotherapy.

- Antioxidant compounds such as glutathione, lipoic acid, and the antioxidant vitamins A, C, and E have been evaluated in this context.

Novel Radioprotectors

- Tetracyclines and fluoroquinolones, which share a common planar ring moiety, were found to be radioprotective by Kwanghee Kim et al. 2009.

- It protect murine haematopoietic stem cells and progenitor cell population from radiation damage.

Mechanism of radioprotector

The following radioprotection mechanisms were proposed:

- 1. Free radical scavenger.
- 2. Repair by hydrogen donation to target molecules.
- 3. Formation of mixed sulfides.
- 4. Delay of cellular division and induction of hypoxia in the tissues.

References

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