29 Radiosensitizers and Radioprotectors

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29.1 Introduction

Radiation therapy is commonly used in most of the solid malignancies in neoadjuvant, adjuvant, definitive, or palliative setting. It damages tumor cells by either direct action (direct DNA damage) or by indirect action (DNA damage by means of free radicals). The goal of radiation therapy is to widen therapeutic ratio by delivering maximum dose to the tumor while at the same time avoiding excessive radiation dose to normal tissues to reduce the side effects. Despite the availability of advanced radiotherapy techniques, normal tissue irradiation always happens.

Although most of the cancer, i.e. head and neck, cervix, prostate, and lymphoma show good response to radiation, there are many cancers which show intrinsic radioresistance, i.e., sarcoma, melanoma, etc. Radioresistance due to hypoxia is also a major issue. Therapeutic ratio can be widened by using agents that selectively sensitize the tumor cells to radiation while protecting the normal tissues from radiation. Radioprotectors are the compounds that are used to decrease the damage to normal tissue caused by radiation. Radiosensitizers are the products that are used to enhance radiation damage to tumor cells [1]. These agents are collectively known as radiation modifiers.

29.2 Radiosensitizers

Radiosensitizers enhance the tumor cell killing without having any altered response of radiation on normal tissue. Radiation dose can be reduced depending on the extent of sensitization. Thus therapeutic ratio is widened with similar tumor control and reduced normal tissue toxicity.

The mechanism of action is mentioned below [2]:

1. Direct enhancement of radiosensitivity of tumor cells
2. Independently cause DNA damage or inhibit DNA double strand break repair
3. Disruption of cell survival pathways
4. Target vasculature of tumor cells
5. Improve oxygenation or selectively act on hypoxic cells
6. Direct cytotoxic action, thus reduce the number of tumor cells required to be killed by radiation
7. Redistribution of the cells in more radiosensitive phase

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29.3 Various Radiosensitizing Agents Are Described Below

Hyperbaric Oxygen Therapy (HOBT) As we know hypoxic cells are radioresistant, numerous trials have been conducted to manipulate hypoxic environment of tumor cells but most of them are inconclusive. Increased oxygen tension in tumor cells just before radiotherapy may lead to increased production of free radicals resulting in cellular damage. However it is cumbersome to put the patient in high pressure oxygen tank before each fraction of radiotherapy. Use of HOBT was started almost 50 years back in a clinical trial by Churchill–Davidson and Foster et al. [3]. Subsequent trials showed improvement in cervical and head and neck cancer patients using HOBT. In a meta-analysis of 32 trials using HOBT in head and neck cancer, improved local control did not turn into improved survival [4].

Carbogen Other strategy to improve oxygen tension in tumor cells is breathing carbogen which is a mixture of 95% oxygen and 5% carbon dioxide at atmospheric pressure. It does not produce vasoconstriction as with 100% oxygen. It is a simple procedure as compared with HOBT [5]. Carbogen is believed to overcome chronic hypoxia and is generally used in combination with Nicotinamide that overcomes acute hypoxia. Nicotinamide is an inhibitor of Poly ADP Ribose polymerase I which repairs single strand DNA break. However results are disappointing in clinical practice.

Metronidazole and Its Analogs Metronidazole and its analogues such as misonidazole, etanidazole, and nimorazole have been shown to increase radiosensitivity of hypoxic tumor cells [6]. These agents are selectively activated in hypoxic environment and act as oxygen and stabilize DNA so that it does not get repaired. Misonidazole deplete sulfhydryl groups in cells and thus inhibiting glycolysis and the repair of radiation-induced damage. Use of misonidazole may lead to CNS side effects. Etanidazole crosses the blood–brain barrier in limited extent and thus CNS side effects are lesser.

Nimorazole also has a better safety profile and thus high dose can be used. Nimorazole has shown to improve 5 year loco-regional control in head and neck cancer as compared to placebo [7].

Tirapazamine Tirapazamine is an agent which is selectively cytotoxic to hypoxic cells. Under hypoxic conditions it reduces to highly reactive product leading to DNA damage. It has been studied in lung and head and neck cancer. Side effects can be nausea, muscle cramps, and hematological toxicities [8]. Mitomycin-C also has selective cytotoxicity to hypoxic cells. It is a bioreductive alkylating agent and has been studied in pancreatic and head and neck cancer.

Hyperthermia Chronically hypoxic cells with a low intracellular Ph and cells in S-phase of cell cycle are considered as radio resistant and are more susceptible to thermal killing. Following are the mechanism of cell killing by hyperthermia [9]:

1. Hyperthermia increases the fluidity of membranes
2. Inhibits the metabolism
3. Inhibition of DNA, RNA, and protein
4. Inhibition of DNA repair
5. Inhibition of repair of sublethal and potentially lethal cellular damage.

Chemotherapeutic Agents Radiosensitization by chemotherapeutic agents is because of various mechanisms. Cisplatin, carboplatin, taxanes, and 5FU are commonest radiosensitizers used with radiotherapy in cervix, head and neck, esophageal and lung cancer. Nedaplatin, approved in Japan, is also radiosensitizer but less nephrotoxic as compared to cisplatin. Cisplatin produces single strand breaks by creating inter- and intrastrand DNA adducts. These single strand breaks are converted to lethal double strand breaks by radiation. Concurrent chemoradiotherapy has shown to be more effective in cervix, head and neck, esophageal and lung cancer as compared to radiotherapy alone. Due to the synergistic action of cisplatin and radiotherapy, a lower dose of each can be used which would be otherwise insufficient to

cause cell death if administered alone. The synergistic effect of cisplatin and radiotherapy is due to below mentioned mechanisms:

1. Increased binding of toxic platinum intermediates in the presence of radiation-induced free radicals
2. Radiation-induced increased cisplatin uptake
3. Cell cycle disruption
4. Inhibition of repair of radiation-induced DNA damage.

5 Fluoro-Uracil (5FU) 5FU is one of the most common drugs used for colorectal cancer treatment and breast cancer. It is an anti-metabolite agent. It also causes radio-sensitization by impairing double strand break repair during the S phase and by acting as free radical scavenger. However, as it is particularly toxic to dividing cells, clinical use is limited by its severe side effects on normal cells. For locally advanced rectal cancer, preoperative 5FU or capecitabine is now considered as the standard of care because of the decreased local recurrence rate and improved survival with addition of 5FU.

Taxanes (Paclitaxel and Docetaxel) Taxanes are microtubule stabilizers and act as radiosensitizer by arresting the cells in G2-M phase.

Topoisomerase Inhibitors: Irinotecan It is a camptothecin derivative that has its cytotoxic effect by targeting topoisomerase I. In addition to having direct cytotoxic effect, these agents have excellent radiosensitization property that may lead to increased cell killing by radiation. Combination of topoisomerase inhibitors and radiation is a new promising approach.

Gemcitabine Gemcitabine is effective as a single agent in variety of solid tumors. The mechanism of radiosensitization by gemcitabine is not clear [10]. However preliminary studies have shown that the radiosensitization with gemcitabine is not because of increase in the radiation-induced DNA double strand breaks. It is said that probably gemcitabine induced radiosensitization is due to apoptosis of the cells undergoing radiotherapy, but the exact mechanism of action is under investigation.

Thymidine analogs The thymidine analogs bromodeoxyuridine and iododeoxyuridine have been used as radiosensitizers in a battery of cancers including head and neck cancers, malignant gliomas, brain metastases, soft tissue sarcomas, intrahepatic cancers, and cervical cancers. These agents produce radiosensitization by incorporating themselves in DNA that increases the DNA susceptibility to single strand breaks from radiation-produced free radicals. However, the adverse effects such as myelosuppression and toxicity in the irradiated area are a concern.

Hydroxyurea It causes cytotoxicity by inhibiting ribonucleotide reductase, an enzyme responsible for the transformation of ribonucleotides to deoxyribonucleotides. It is often used to treat hematologic malignancies and myeloproliferative disorder [11]. Its use as a radiosensitizer is investigated since 1960s in patients with head and neck cancer, malignant glioma, and cervical cancer. Since it has no cytotoxicity for these tumors, any positive result is assumed to be because of radiosensitization.

Membrane Active Agent Cell membrane is also a critical target for cell killing. Drugs such as local anesthetic (procaine and lidocaine hydrochloride) and tranquilizers (chlorpromazine) interact with cell membranes and alter their structural and functional organization. These drugs have been observed to increase the radiosensitivity in Escherichia coli under hypoxic conditions. These drugs have been observed to enhance radiosensitivity of hypoxic mouse lymphoma cells while radioprotection of these cells was seen under euoxic conditions.

Sulfhydryl Group Suppressor Intracellular compounds containing sulfhydryl (thiol) groups are known to have radioprotective properties. Thus depletion of these compounds may increase the radiosensitivity. Glutathione is the major intracellular sulfhydryl compound. N-Ethylmaleimide, diamide, and diethylmaleate

deplete the glutathione level and thus increase radiosensitivity. Decrease in the glutathione content also inhibits the repair of single strand DNA breaks under aerobic conditions [12].

PARP inhibitors are also believed to increase radiosensitization by targeting DNA damage, endothelium, and tumor vasculature in pre-clinical studies. However, implementation of these results in actual clinical scenario is not known yet.

29.4 Radioprotectors

Other than sensitizing the tumor cells to radiation, protection of normal tissues from radiation injury is also an approach to widened therapeutic ratio. Radiation protectors protect normal tissue from deleterious effect of radiation, making a potential for radiation escalation and thus improvement in therapeutic ratio. Both acute and late toxicities can be reduced as these agents limit the initial extent of tissue damage.

Radiation exposure to normal tissue is an inevitable event which may lead to a battery of side effects ranging from mild symptoms to life threatening complications. Radiation related toxicity depends on many factors such as dose, volume fractionation, overall treatment time, and intrinsic radiosensitivity. Although advanced radiation techniques such as Intensity Modulated Radiotherapy (IMRT), image-guided radiotherapy, and proton radiotherapy have been shown to reduce these toxicities, intrinsic radiosensitivity of the cells is a component which cannot be taken care with these technologies. This is why radioprotectors are important.

Radioprotector agents should have the following characteristics:

1. It should not protect tumor cells
2. It should have minimal toxicity
3. Easy administration.

Mechanism of Action of Radioprotectors Majority of these agents prevent DNA damage by scavenging free radicals. Radioprotectors should have the capacity of entering the nucleus of the cell and to reside near the DNA because free radicals have very short life and range [2].

Although many agents have been identified as radiation protectors in preclinical stages, only Amifostine and Nitroxides have been found to be useful. In clinical setting only, Amifostine is the FDA approved agent; however, tumor protection is a controversial issue with this. Antioxidants also have shown to have some radioprotector properties [13].

Amifostine (WR-2721) It is the most widely used radioprotector as it has been shown to concentrate less in tumor tissue as compared to normal tissue probably due to tumor acidosis and lower expression of alkaline phosphatase in tumor cells. It is known to induce hypoxia in the tumor cells and causes DNA condensation [14]. It is an inactive drug and converts to active thiol by dephosphorylation by alkaline phosphatase in normal endothelium. In the dephosphorylated state, it enters into the cells and scavenges free radicals responsible for tissue injury. Studies have shown that it significantly reduces moderate to severe xerostomia in head and neck patients who receive postoperative radiotherapy. Other than xerostomia, it also protects lungs, bone marrow, heart, intestines, and kidneys and provides protection in cisplatin induced nephrotoxicity, ototoxicity, and neuropathy and cyclophosphamide induced hematologic toxicity. However 2008 ASCO guidelines state that due to concern of tumor protection, the routine use of amifostine in these settings is not recommended. Side effects of amifostine can be hypotension, nausea, vomiting, dizziness, sneezing, hot-flashes, hypocalcemia, and mild somnolence.

Antioxidants as Radioprotectors As side effects of radiotherapy imitate oxidative damage, antioxidants (Vitamin A, C, E, glutathione, lipoic acid) are believed to protect the normal cells against radiation [15]. *Nitroxide* also has unique antioxidant properties and is another promising agent for future use as radiation protectors. However as with amifostine, there is a risk of tumor protection due to non-selective free radical scavenging. The use of antioxidant vitamins during the course of radiotherapy was associated with poor tumor control in head and neck cancers.

Superoxide dismutase (SOD) is an antioxidant enzyme which is present in human cells. Ionizing radiation leads to formation of highly reactive superoxide radicals that has a potential of cellular damage. SOD acts as an antioxidant and catalyzes the conversion of superoxide to oxygen and hydrogen peroxide. Animal models have been used for gene therapy to increase SOD expression in tissue expected to receive radiation [16].

Melatonin is also an antioxidant and increases the expression of antioxidant enzymes i.e. SOD and glutathione peroxidase.

Alpha-Tocopherol/Vitamin E (Vit E) VE containing gargles before radiotherapy and 8–12 h after radiotherapy has been shown to reduce the incidence of oral mucositis in patients who received radiotherapy for oral cavity and oropharyngeal cancers.

Radiation Mitigators These are the agents that function after initial exposure to radiation and thus limit late radiation injury such as fibrosis. Pentoxifylline and vitamin E are the examples which have been used to treat cutaneous fibrosis after breast radiotherapy.

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