Journal of Research in Applied and Basic Medical Sciences 2021; 7(3): 161-171

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

The Role of Radioprotector Agents in the Protection of Normal tissue

Soraya Emamgholizadeh Minaei[1]

[1] *Assistant Professor of Medical Physics, Department of Medical Physics and Imaging, Urmia University of Medical Sciences, Urmia, Iran*

***Corresponding authors:** Soraya Emamgholizadeh Minaei, **Address**: Department of Medical Physics and Imaging, Urmia University of Medical Sciences, P.O.Box: 5756115198, Urmia, Iran, **Email**: minayee.s@gmail.com, emamgholizadeh.s@umsu.ac.ir, **Tel**: +984432752300,

Abstract

The role of radioprotectors to reduce the cellular damage induced by ionizing radiation has been studied in human, animal and in vitro culture models. Radiation therapy cannot eradicate tumors successfully because of soft tissue damage. Proper use of radioprotective agents (before or shortly after radiation) can reduce normal tissue radiation toxicity and improve treatment output. There are three groups of radioprotectors: Synthetic protectors, antioxidant nutrients, and Immunomodulators. We discussed the radioprotective efficacy and its interaction against toxic agents. In addition, we discussed articles that have used radioprotective agents in the treatment of cancer with radiotherapy to protect normal tissue.

***Keywords*:** Radio protectors, Free radical, Antioxidant, Toxic substances, Radical scavenger

Received 02 August 2021; accepted for publication 17 November 2021

Introduction

In normal cellular metabolism, free radicals or reactive oxygen species (ROS) are usually produced, but they are not dangerous because their effects are balanced by an endogenuous repair system. Levels of ROS can be elevated by deficiencies in the cellular metabolism or by exposure to oxidative stress such as ionizing radiation (X-ray, gamma ray, β^-, α or proton) (1). Exposure to ionizing radiation (IR) is associated with the production of free radicals and toxic substances that can damage crucial macromolecules, structures (such as DNA, cell membranes, and enzymes), and cause cell death. IR can remove electrons from outer orbital of atoms to form ions. Damages caused by IR can be direct and indirect. Although the direct damage observed during exposure to low linear energy transfer (LET) radiation (such as X-ray or gamma ray) is low, but the effect is increased for high LET radiation (such as α particles) (2).

Since the body is primarily composed of water, low LET radiation interact with water and produce reactive free radicals (OH^0, H^0, …) that cause side effects of IR (2,3). The effect of radioprotectors to reduce the normal cellular toxicity induced by ionizing radiation has been studied in animal and in vitro culture models for many years (3-6). The application of radioprotectors to various human exposure situations has not been extensive. The complete treatment of cancer requires specific strategies that can eradicate tumors without damage to normal soft

tissues. Conventional therapies generally were unsuccessful to eradicate cancer absolutely because of normal soft tissue injuries. To reduce normal tissue damage, specific strategies are utilized such as Intensive-modulated radiotherapy (IMRT), conformal radiotherapy, proton radiotherapy, and protection of normal tissues with radioprotective agents.

Indirect damages caused by free radicals and peroxides can lead to significant cellular injuries or cell death, particularly in sensitive cells (such as hematopoietic, lymphoid tissues, and gastrointestinal system). Therefore, the administration of radioprotectors to body before or shortly after radiation can scavenge free radicals in normal tissues and protect them against radiation damages (7). But radioprotectors absorbed by tumor cells can protect them against radiation. In addition, further studies are required to determine potential of radioprotectors during radiotherapy for the treatment of cancer (8).

2. Radiation interaction

Ionizing radiation consists of both electromagnetic (gamma rays or X-rays) and particulate radiations (electrons, protons, neutron, or alpha particles). If the radiation has sufficient energy to eject the electron from the atom or molecules, the radiation is referred to as ionizing radiation and can ionize the atom (9). Following ionization, reactive oxygen species (ROS), free radicals (OH^0, H^0), and other toxic substances (such as H_2O_2) are produced. Reactive oxygen species interact with the macromolecules (DNA, proteins, and lipids) and can induce DNA damage. DNA damage is the most important factor in cell death and dysfunction of the cells (10).

In normal tissue, there is a balance between producing free radicals and scavenging of them. Endogenous enzymes in cells (such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX)) are able to detoxify and remove free radicals from cells before they can attack crucial molecules. But when these free radicals increase in cells following exposure to radiation, endogenous enzymes are not able to protect the cell against free radicals. Therefore, for the protection of normal tissues and to decrease the side effect of radiation, the use of other radiation modulators is needed.

3. Classification of radioprotectors

The function of radioprotective agents in reducing the side effects of normal tissues is different. Some of them induce hypoxia in cells and by consumption of oxygen, decrease the level of free radicals (1). The mode of action of another class of radioprotective agents is the stimulation and proliferation of hematopoietic stem cells. These agents stimulate cells and release cytokines that stimulate pluripotent cells in bone marrow. This class of radioprotective agents is referred to as Immunomodulators. So far, many compounds have been evaluated as radioprotective agents in animal, cell culture, and human experiments (11, 12).

Generally, radioprotectors are divided into three groups:

1) Synthetic Radio protectors
2) Immunomodulators
3) Antioxidants

3.1. Synthetic Radio protectors

Since 1949 some Synthetic chemical compounds were introduced that could protect biological systems against the radiation. This group of compounds have thiol group (SH) and make the maximum radioprotection. Amifostine is one of these compounds that has the best efficiency and it is related to the target organ and creates a high dose reduction factor (DRF) against the low LET radiation (10). The function of these radioprotectors is through radical scavenging, hydrogen donation, inducing hypoxia, and DNA Stabilization (6, 13-15). Some of the synthetic chemical compounds are phosphorothioates, mercaptans di-, trisulfides, Amifostine, thiazolidines, imidazoles, mizonidazole, benzofurans acid hydrozides, alcohols, and so on.

3.2. Immunomodulators

The hematopoietic system is very sensitive against the radiation. Delivering a high dose of radiation inhibits the function of this system. Blood ingredients will be less and its complications (infection and anemia) become

apparent. Immunomodulators are compounds that stimulate hematopoietic stem cells and progenitor systems that induce their growth, proliferation, and differentiation of them. Immunomodulators increase the level of different cytokines that are required for hematopoietic recovery and proliferation of them (16). Applying cytokines and growth factors also induce stimulation of hematopoietic system. Cytokines are more effective when applied with other cytokines or radioprotectors and have synergistic radio protectiveness. Cytokines also have radiosensitizing effect. This opposite effect relates to induction or inhibition of progenitor cell cycling that can be induced by different treatment schedules (4).

Glacan (a kind of solvable polysaccharides) (17), Endotoxin (18), ginseng root extract (16), oxymetholone (as an anabolic-androgenic steroid), and 5-androstendiol (AED) are natural immunomodulator compounds (19, 20). However, Azimoxin (5), diethyldithiocarbamate (DDC), and levamisole are synthetic immunomodulators (21).

3.3. Antioxidants

The development of high radioprotective agents with low toxic side effects is desirable. Natural compounds like antioxidants can be more effective than other radioprotectors. Antioxidant mechanisms act through catching and trapping free radicals by thiol and aromatic groups. Some antioxidants including Vitamins A, E, C (22, 23), tocopherol monoglucoside (soluble form of vitamin E) (24), Glutathione (GSH) are modified forms of cycteine, sulfhydryl compound, Melatonin that is produced in pineal gland (25), Flavonoids that are in fruits (26, 27), and Minerals like selenium and copper.

Recently herbal extracts are studied for radioprotection. This agent causes low DRF but in radioprotective doses have a low toxic effect. They have antioxidant and immunomodolator effects.

4. The criteria of ideal protective agent

Over the past several years, many compounds were examined to find effective radioprotector with low toxicity and side effects (8). Early attempts to use thiol began with the introduction of cysteine. More than 4,000 compounds have been studied so far. The ideal radioprotective agent should have several criteria (14):

1. Scavenge free radicals and be an antioxidant.
2. Increase the activity of antioxidant enzymes in the body.
3. Have a selective protective effect on normal tissue, without a protective effect on tumor cells.
4. Have an active effect on the proliferation of hematopoietic stem cells.
5. It must be a stable compound in the body with a long half time.
6. Have an acceptable route for administration (such as oral, subcutaneous, or intramuscular).

But so far, no radioprotective agents meet all of these criteria and most of them are not used because of their side effects. Many researchers have studied ideal radio protective compounds that have more efficacy, low toxicity, and an acceptable route for administration. In recent years, so many radioprotective agents have been examined for their ability to decrease radiation-induced damage in normal cells.

5. Examples of common radioprotectors

5.1. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is the secretary product of the pineal gland, it is lipophilic and somewhat aqueous soluble (28, 29). In the darkness at night, its concentration is in the maximum level (30, 31). Many investigations (in vitro, in vitro/in vivo, in vivo, and clinical studies) were carried out about the protective effect of melatonin, they have documented that melatonin is a radical scavenger, an antioxidant, and immunomodulator agent (25). Melatonin administration is easy because it is absorbed through any route especially oral route.

Vijayalaxmi et al. investigated the radioprotective effect of melatonin in vitro, in vitro/in vivo, and in vivo conditions. They cultured human blood lymphocytes, and treated them with various concentrations of melatonin for 20 minutes, after that the samples were exposed to 150 cGy gamma radiation. They observed a significant reduction (about 60%) in the frequency of

micronuclei as compared to samples that were not treated with melatonin (25). In another study (32), blood samples were collected at 1 and 2 hours after melatonin administration (300mg) after that samples were exposed to 150 cGy gamma radiation. Finally, they exhibited a significant reduction (60-65%) in the incident of chromosomal aberrations and micronuclei as compared to samples before melatonin administration. The best protective effect was observed 2 hours after administration.

Moreover, Shirazi et al. (33) administered 30 mg/kg of melatonin for 30 min before whole-body radiation to mice. Moreover, mice received 30 mg/kg melatonin for three days after radiation. They showed that radiation alone caused liver injuries (malondialdehyde (MDA) level increased and glutathione (GSH) level decreased). However, administration of melatonin before and after radiation reduced liver damages caused by radiation (Figure 1). Therefore, in their study, the radioprotective effect of melatonin was also confirmed.

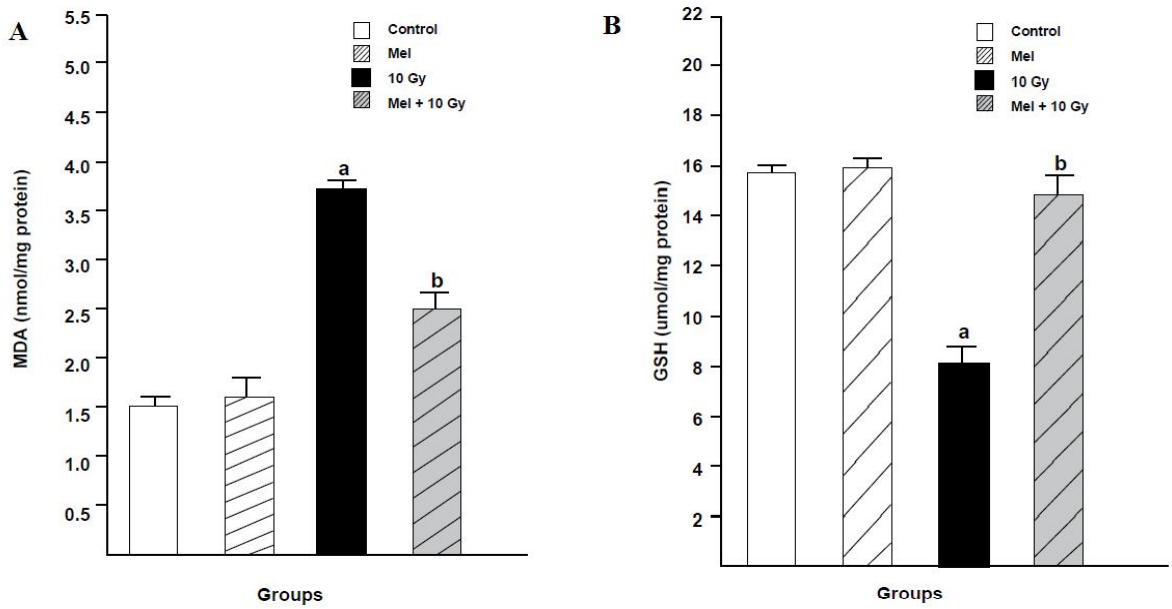

Fig 1. Radioprotection effect of melatonin on the radiation-induced damage. (A) The level of malondialdehyde (MAD). (B) The level of glutathione (GSH) in rats. a: $p<0.05$ (compared to the control group) and b: $p<0.05$ (compared to the radiation groups) (33).

Blickenstaff et al. (34) found that exposure to 950 cGy of whole-body radiation caused the death of all animals within 12 days, while 43% of mice that were treated with melatonin (1.076 mM/kg) before the exposure survived at least 30 days after exposure of lethal dose of radiation.

5.2. Nitroxide radicals

Nitroxide radicals are unstable chemical compounds that look like conventional radicals, but cyclic nitroxide compounds are stable. For example, 2, 2, 6, 6-tetra methypiperidine-1-oxyl (Tempol) is a stable radical (35). Since they have been known as compounds which can interact with free radicals, they are used as biophysical tools. Lots of In Vitro investigations have proved that these compounds can scavenge ROS. It has been proven that nitroxide in special conditions interacts with metal ions of DNA structure and subsequently restrains them from incorporating to convert H2O2 to OH^0. Furthermore, consumption of O^{-2} by nitroxide inhibits the reduction of oxidized metal ions in DNA. Other mechanisms are induction of hypoxia inside the cells and scavenging the toxic compounds produced by radiation (36, 37). These compounds protect cells in

hypoxic conditions, not in oxygenated conditions. But nitroxide faces some obstacles In Vivo condition including nonspecific dispersion in normal tissue, high renal clearance, and rapid reduction of nitroxide to hydroxylamine (its non-protective analogue).

Mitchel et al. (38) conducted an investigation to evaluate the radiation protection effect of Tempol-H on hamster V29 cells after radiation. Cells were treated with Tempol-H in final concentration of 5, 10, 50 and 100 mM for 10 min prior to radiation. Immediately after radiation, the medium was diluted and the cells were grown for clonogenicassay. The results showed that Tempol-H as a nonthiol radioprotector can protect mammalian cells from radiation-induced injury.

In another study, which was run by Hahn et al. (35), the radioprotective effect of Tempol-H was assessed on RIF1 tumor cells implanted into mice. First, they implanted the tumoral cell into mice and 10 days later 275mg/kg of Tempol-H or PBS was injected intraperitoneally. The survival curve of cells was drawn after 10 and 33 Gy radiation. No significant difference was found between the mice treated with Tempol-H or PBS.

The difference in radioprotection effect of nitroxide can be due to the bio-reduction rate of nitroxide to hydroxylamine (its non-protective analogue) in different cells.

5.3. Rosemary

Rosemary is a famous species of Lamiaceae family originated from the Mediterranean region. It grows up to 1 meter high and has got blue flower with dark green leaves. Rosemary has been shown to have extensive biological activity due to its antioxidant properties. Rosemary extract after administration can increase GSH level in the blood. Furthermore, it restrains lipid peroxidation after radiation (39). An interesting point is that the treatment with rosemary before radiation can lead to a higher degree of protection rather than after radiation. Soyal et al. (40) investigated the effect of rosemary extract on radiation-induced hepatic injury in mice. Mice were divided into 2 groups (control and experimental). In both groups, the number of abnormal cells increased after 6 Gy radiation but in experimental group treated with 1000mg/kg rosemary extract, the number of abnormal cells decreased after 10 days (40). Another study was done on blood cells of mice by Jindal et al. They administered 1000 mg/kg of rosemary extract orally and exposed the mice to 3 Gy radiation. It was found that the number of erythrocyte and leucocyte counts, hemoglobin content and hematocrit percentage decreased while a significant increase was observed in the experimental group by the day of 30 post-treatment (41).

5.4. Vitamins (C&E)

These vitamins are known as antioxidant nutrients. Vitamin C (ascorbic acid) is an essential material in different species of humans and plants. It is produced by most of the organisms especially mammalian and acts as water-soluble antioxidant in oxidative stress (42).

Vitamin E refers to a group of fat-soluble compounds. There are many different forms of vitamin E that α-tocopherol is the most biologically active form. This vitamin also has antioxidant properties. Vitamin E protects chain reaction of lipid peroxidation in cell membranes by two mechanisms: either it reacts with unsaturated fatty acid or protects polypeptide chains. Vitamin E scavenges oxygen molecules, peroxide, and hydroxyl radicals while vitamins C scavenges oxygen molecule, hydroxyl radicals, and atomic oxygen radicals. Effecting points of these vitamins are different. Vitamin E is effective on membrane of all cells, nucleus, endoplasmic reticulum and mitochondria whereas vitamin C as a water-soluble vitamin is effective on cytoplasm and lysosome (43, 44).

Felemovicus et al. (45) evaluated the effect of vitamin E on the small bowel of rat. They filled the small bowel with vitamin E solution through a surgery then exposed them to 11Gy X_ray. Five days later the mice were sacrificed and the surviving crypts, mucosal height and goblet cell preservation were compared with the control group. All the parameters were significantly protected from radiation. Soheir et al. (44) conducted another study and evaluated the effect of vitamin C and E on chromosomal aberrations in albino rats. Rats were fed

by aqueous vitamin C and E solution for 6 months. Then they were exposed to whole-body radiation. After killing the rats the chromosomal aberrations were recorded. They concluded that vitamin C was more effective than vitamin E.

5.5. Lycopene

Lycopene is a carotenoid, which is produced by plants and microorganisms. It is found especially in red fruits, tomatoes, and vegetables (46). Lycopene has a structure similar to antioxidant beta-carotene, but its antioxidant activity is much stronger. It reduces the effects of radiation by antioxidant and free radical scavenging ability (47, 48). Lycopene increases the levels of the antioxidant enzymes, and these enzymes scavenge ROS. It also inhibits peroxidation of membrane lipids.

Srinivasan et al. evaluated the radioprotective effect of lycopene on rat hepatocytes using cytogenetic and biochemical methods (47, 49). They found that the frequency of chromosomal aberration and peroxidation of lipids in samples pretreated with lycopene were lower. Lycopene caused a reduction in the frequency of micronuclei, dicentromic chromosome, the level of thiobarbituric acid reactive substances (TBARS), and hydroperoxides (HP); it also increased the level of antioxidant enzymes (GSH, SOD, CAT, and GPX) (47, 49). In this paper, the best dose of lycopene for protection was 5µgr/ml (49).

Cavusoglu et al. (50) have exhibited radioprotective effect of lycopene in human lymphocytes by metaphase analysis. They collected samples and cultured them, then pretreated with various doses of lycopene (0.001, 0.005, 0.01, 0.015, 0.018 and 0.02 µM), after that samples were exposed to 10 Gy gamma rays for 30 minutes. They found that the level of chromosomal aberration in the presence of lycopene (especially at 0.01, 0.015, 0.018 µM concentrations) was lower than the samples treated with lycopene.

5.6. Cimetidine/Ranitidine/Famotidine

Cimetidine, Ranitidine, and Famotidine are histamine H_2 receptor antagonists and are used for peptic ulcer treatment. These drugs are economical, not expensive and available in the market, and also they can be administrated orally.

Investigators have demonstrated that cimetidine is an immunomodulator and radical scavenger agent, but ranitidine and famotidine are only radical scavenger agents (51, 52). Cimetidine increases the frequency ofCD_4^+ lymphocytes (effector T cells) and inhibits T suppressor cells. This process causes the production of glutathione reductase and catalase enzymes, which prevents DNA damage. Therefore, Cimetidine reduces the effects of radiation through radical scavenging method via catalysis enzymes (52, 53). Famotidine and ranitidine, especially famotidine, scavenge hydroxyl radical (OH^0), HOCl, and NH_2Cl. Famotidine scavenges OH^0 about 10-fold higher than that of Manitol (3, 51, 54).

Mozdarani et al. have conducted several studies about the radioprotective effect of these drugs. They investigated radioprotective ability of cimetidine, ranitidine, and famotidine in vitro and in vivo conditions by micronuclei assay and metaphase analysis (3). In micronuclei assay, mice were intraperitoneally injected at various concentrations of cimetidine, ranitidine, and famotidine (Table 1), for 2 hours before 2 Gy radiation. 24 hours after treatment, then they sacrificed the mice and femoral bone marrow was flushed. Moreover, in metaphase analysis blood samples were collected and treated with these drugs (100µmol/Lit) for 1h before 3Gy gamma radiation. The results in both methods were the same. They exhibited that all drugs reduce the frequency of chromosomal aberrations and micronuclei with DRF of 1.35 - 1.95. Famotidine was more effective than cimetidine and ranitidine with DRF of 1.95. Famotidine and Ranitidine were more effective than cimetidine at lower concentrations (3) (Table1).

Table 1: DRF values for cimetidine, ranitidine, and famotidine in two methods (3)

Drug	Dose	DRF
In vivo treatment		
Cimetidine	7.5 mg/kg	1.35

	15 mg/kg	1.61
Ranitidine	2.5 mg/kg	1.81
	5 mg/kg	1.89
Famotidine	0.75 mg/kg	1.56
	1.5 mg/kg	1.95
In vitro treatment		
Cimetidine	100µmol/lit	1.45
Ranitidine	100µmol/lit	1.52
Famotidine	100µmol/lit	1.95

In another study, Mozdarani et al. have also exhibited the effect of cimetidine and famotidine on the survival of mice. Mice were exposed to different doses of radiation and then LD50/30 was calculated (723.7cGy). In another group, mice took different doses of cimetidine and famotidine in combination with 801cGy gamma irradiation and then the best protecting concentration of drugs was found [10 mg/kg for famotidine and 15 mg/kg for Cimetidine] (55). Finally, mice were treated with these doses of drugs in combination with various doses of gamma rays (528-801cGy) and DRF was calculated using the LD50/30 in each group. DRF for optimum dose of cimetidine and famotidine were 1.11 and 1.05, respectively (55). In this article, DRF of cimetidine was more than famotidine unlike other studies. Immunomodulatory ability of cimetidine might be the cause of this effect.

Razzaghdoust et al. (56) in a phase I/II randomized clinical trial study evaluated 36 patients with prostate cancer. Patients received 40 mg famotidine or placebo twice daily 3 and 4 h prior to radiotherapy. Then, bowel and bladder acute toxicity were evaluated according to RTOG toxicity grading criteria. The results showed that there was no significant difference between two groups in the toxicity of urinary. However, rectal toxicity in the group treated with famotidine was significantly lower than that of placebo group (Figure 2). Therefore, their study proved that the administration of famotidine before radiotherapy for the prostate cancer patients could reduce the radiation-induced toxicity on rectal mucosa.

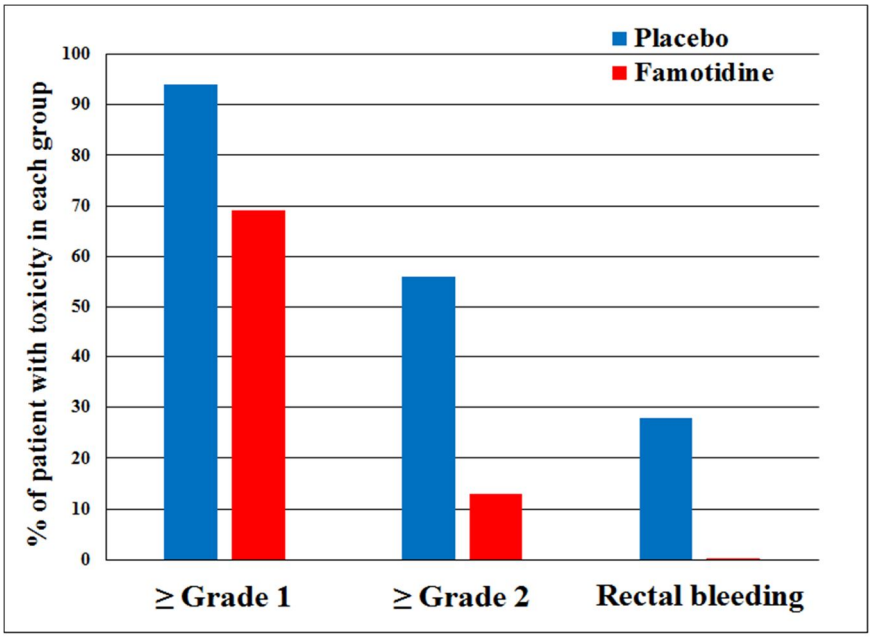

Fig 2. Radiation-induced rectal toxicity (according to RTOG toxicity grading criteria) in prostate cancer patients treated with famotidine or placebo before radiotherapy (56).

5.7. Amifostine

S-2-(3-aminopropylamino) ethylphosphorothioic acid or Amifostine, is one of the amino thiols compounds that contain cysteine and thiol. Amifostine is the most effective Radio protector and it has a protection factor of 2.8. First, it is phosphorylated spontaneously or by alkaline phosphatase enzyme and conform to WR-1065 (its active form). Amifostine provides protection against ionizing radiation by free radical scavenging, hydrogen donation, inducing hypoxia, and DNA Stabilization (57). It is illustrated that thiol agent is probably activated by oxygen, so it causes hypoxia and radiation protection in the tissue. Amifostine protects bone marrow, immune system, skin, small intestine, colon, lung, esophagus, kidney, salivary glands, oral mucosa, and testes with various dose reduction factors. The major protection of Amifostine is related to bone marrow and salivary glands, but brain is not protected by Amifostine. Amifostine has side effects in therapeutic doses including hypotension, hypocalcemia, renal complication, disorder in temperature, nausea, drowsiness, losing weight, and vomiting. In the clinical trial study, it has been shown that Amifostine was able to reduce acute and chronic xerostomy incidence induced by head and neck radiotherapy (58).

In one randomized phase III clinical trial, the radio-protective effect of Amifostine on cancer was evaluated. In this study, 300 patients with head and neck cancer received 200mg/m2 of Amifostine for 15-30 min before radiotherapy. The results indicated that daily use of Amifostine significantly reduced the incidence of acute and chronic xerostomia without disordering the efficacy of radiotherapy, but it did not diminish acute mucositis. It had side effects like allergic reactions, nausea, and vomiting (59).

6. Conclusion

Radiation therapy cannot eradicate tumor successfully because of soft tissue damage. Radioprotectors can reduce normal tissue damage. Proper use of radioprotective agents (before or shortly after radiotherapy) can reduce normal tissue radiation toxicity and improve the treatment output and therapeutic ratio. The important point that should be considered is the possibility of resistance induction by radioprotectors in clinical trials. Among the mentioned radioprotectors, Amifostin is the only radioprotective agent that is currently used in clinical settings. Research still continues on the use of other radioprotectors (especially melatonin and famotidine) in the clinical trials.

7. Declaration of Interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper

Conflict of interest

The authors have no conflict of interest in this study.

References

1. Hosseinimehr SJ. Flavonoids and genomic instability induced by ionizing radiation. Drug Discov Today 2010;15(21-22):907-18.
2. Hunter N, Muirhead CR. Review of relative biological effectiveness dependence on linear energy transfer for low-LET radiations. J Radiol Prot 2009;29(1):5.
3. Mozdarani H. Radioprotective Properties of Histamine H 2 Receptor Antagonists: present and future prospects. J Radiat Res 2003;44(2):145-9.
4. Singh VK, Yadav VS. Role of cytokines and growth factors in radioprotection. Exp Mol Pathol 2005;78(2):156-69.
5. Bicker U, Friedberg K, Hebold G, Mengel K. Reduction of acute toxicity of cyclophosphamide and X-rays by the new immunomodulating compound BM 12.531. Experientia 1979;35(10):1361-3.
6. Cassatt DR, Fazenbaker CA, Bachy CM, Hanson MS, editors. Preclinical modeling of improved amifostine (Ethyol) use in radiation therapy. Seminars in radiation oncology: Elsevier; 2002.
7. Citrin D, Cotrim AP, Hyodo F, Baum BJ, Krishna MC, Mitchell JB. Radioprotectors and mitigators of radiation-induced normal tissue injury. Oncologist 2010;15(4):360-71.
8. Schmidt-Ullrich RK. Molecular targets in radiation oncology. Oncogene 2003;22(37):5730.

9. Harborne JB, Williams CA. Advances in flavonoid research since 1992. phytochemistry 2000;55(6):481-504.
10. Brown DQ, Pittock III JW, Rubinstein JS. Early results of the screening program for radioprotectors. Int J Radiat Oncol Biol Phys 1982;8(3-4):565-70.
11. Hosseinimehr SJ. Trends in the development of radioprotective agents. Drug Discov Today 2007;12(19-20):794-805.
12. Koukourakis MI, Kyrias G, Kakolyris S, Kouroussis C, Frangiadaki C, Giatromanolaki A, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. J Clin Oncol 2000;18(11):2226-33.
13. Livesey JC, Reed DJ. Chemical protection against ionizing radiation. Adv Radiat Biol 1987;13:285-353.
14. Maisin J-R. Bacq and Alexander award lecture chemical radioprotection: past, present and future prospects. Int J Radiat Biol 1998;73(4):443-50.
15. Held KD, Biaglow JE. Mechanisms for the oxygen radical-mediated toxicity of various thiol-containing compounds in cultured mammalian cells. Radiat Res 1994;139(1):15-23.
16. Song J-Y, Han S-K, Bae K-G, Lim D-S, Son S-J, Jung I-S, et al. Radioprotective effects of ginsan, an immunomodulator. Radiat Res 2003;159(6):768-74.
17. Patchen ML. Immunomodulators and hemopoiesis. Surv Immunol Res 1983;2(3):237-42.
18. Ainsworth E, Larsen R, Mitchell F, Taylor J. Survival-Promoting Effects of Endotoxin in Mice, Dogs, and Sheep. Naval Radiological Defense Lab., San Francisco; 1970.
19. Stickney DR, Dowding C, Garsd A, Ahlem C, Whitnall M, McKeon M, et al. 5-androstenediol stimulates multilineage hematopoiesis in rhesus monkeys with radiation-induced myelosuppression. Int Immunopharmacol 2006;6(11):1706-13.
20. Stickney DR, Dowding C, Authier S, Garsd A, Onizuka-Handa N, Reading C, et al. 5-androstenediol improves survival in clinically unsupported rhesus monkeys with radiation-induced myelosuppression. Int Immunopharmacol 2007;7(4):500-5.
21. Milas L, Hunter N, Ito H, Peters LJ. In vivo radioprotective activities of diethyldithiocarbamate (DDC). Int J Radiat Oncol Biol Phys 1984;10(12):2335-43.
22. Aruoma OI. Free radicals, oxidative stress, and antioxidants in human health and disease. J Am Oil Chem Soc 1998;75(2):199-212.
23. Seed T, Kumar S, Whitnall M, Srinivasan V, Singh V, Elliott T, et al. New strategies for the prevention of radiation injury: possible implications for countering radiation hazards of long-term space travel. J Radiat Res 2002;43(S):S239-S44.
24. Satyamitra M, Devi PU, Murase H, Kagiya VT. In vivo radioprotection by α-TMG: preliminary studies. Mutat Res 2001;479(1-2):53-61.
25. Reiter RJ, Tan D-X, Herman TS, Thomas Jr CR. Melatonin as a radioprotective agent: a review. Int J Radiat Oncol Biol Phys 2004;59(3):639-53.
26. Devi PU, Ganasoundari A, Rao B, Srinivasan K. In vivo radioprotection by ocimum flavonoids: survival of mice. Radiat Res 1999;151(1):74-8.
27. Uma Devi P, Ganasoundari A, Vrinda B, Srinivasan K, Unnikrishnan M. Radiation protection by the ocimum flavonoids orientin and vicenin: mechanisms of action. Radiat Res 2000;154(4):455-60.
28. Landauer MR, Srinivasan V, Seed TM. Genistein treatment protects mice from ionizing radiation injury. J Appl Toxicol 2003;23(6):379-85.
29. Cavallo A, Hassan M. Stability of melatonin in aqueous solution. J Pineal Res 1995;18(2):90-2.
30. Snyder SH, Axelrod J, Zweig M. Circadian rhythm in the serotonin content of the rat pineal gland: regulating factors. J Pharmacol Exp Ther 1967;158(2):206-13.
31. Claustrat B, Geoffriau M, Brun J, Chazot G. Melatonin in humans: a biochemical marker of the circadian clock and an endogenous synchronizer. Neurophysiol Clin 1995;25(6):351-9.
32. Reiter RJ, Herman TS, Meltz ML. Melatonin and radioprotection from genetic damage: in vivo/in vitro studies with human volunteers. Mutat Res 1996;371(3-4):221-8.
33. Shirazi A, Mihandoost E, Ghobadi G, Mohseni M, Ghazi-Khansari M. Evaluation of radio-protective effect of

melatonin on whole body irradiation induced liver tissue damage. Cell J Yakhteh 2013;14(4):292.

34. Blickenstaff RT, Brandstadter SM, Reddy S, Witt R. Potential radioprotective agents. 1. Homologs of melatonin. J Pharm Sci 1994;83(2):216-8.
35. Hahn SM, Sullivan FJ, DeLuca AM, Krishna CM, Wersto N, Venzon D, et al. Evaluation of tempol radioprotection in a murine tumor model. Free Radic Biol Med 1997;22(7):1211-6.
36. Chung SI, Smart DK, Chung EJ, Citrin DE. Radioprotection as a method to enhance the therapeutic ratio of radiotherapy. Increasing the therapeutic ratio of radiotherapy: Springer; 2017. p. 79-102.
37. Kamran MZ, Ranjan A, Kaur N, Sur S, Tandon V. Radioprotective agents: strategies and translational advances. Med Res Rev 2016;36(3):461-93.
38. Mitchell JB, DeGraff W, Kaufman D, Krishna MC, Samuni A, Finkelstein E, et al. Inhibition of oxygen-dependent radiation-induced damage by the nitroxide superoxide dismutase mimic, tempol. Arch Biochem Biophys 1991;289(1):62-70.
39. Del Bano M, Castillo J, Benavente-García O, Lorente J, Martín-Gil R, Acevedo C, et al. Radioprotective− Antimutagenic Effects of Rosemary Phenolics against Chromosomal Damage Induced in Human Lymphocytes by γ-rays. J Agric Food Chem 2006;54(6):2064-8.
40. Soyal D, Jindal A, Singh I, Goyal P. Protective capacity of Rosemary extract against radiation induced hepatic injury in mice. Int J Radiat Res 2007; 4(4): 161-8.
41. Jindal A, Soyal D, Sancheti G, Goyal PK. Radioprotective potential of Rosemarinus officinalis against lethal effects of gamma radiation: a preliminary study. J Environ Pathol Toxicol Oncol 2006;25(4):633-42.
42. Zangeneh M, Mozdarani H, Mahmoudzadeh A. Potent radioprotective effects of combined regimens of famotidine and vitamin C against radiation-induced micronuclei in mouse bone marrow erythrocytes. Radiat Environ Biophys 2015;54(2):175-81.
43. Mortazavi S, Rahimi S, Mosleh-Shirazi M, Arjomandi M, Soleimani A, Hossein-Abadi OK, et al. A comparative study on the life-saving radioprotective effects of vitamins a, E, C and over-the-counter multivitamins. Journal of biomedical physics & engineering. 2015;5(2):59.
44. El-Nahas SM, Mattar FE, Mohamed AA. Radioprotective effect of vitamins C and E. Mutat Res Lett 1993;301(2):143-7.
45. Felemovicius I, Bonsack ME, Baptista ML, Delaney JP. Intestinal radioprotection by vitamin E (alpha-tocopherol). Ann Surg 1995;222(4):504.
46. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. J Natl Cancer Inst 1999;91(4):317-31.
47. Srinivasan M, Sudheer AR, Pillai KR, Kumar PR, Sudhakaran P, Menon V. Lycopene as a natural protector against γ-radiation induced DNA damage, lipid peroxidation and antioxidant status in primary culture of isolated rat hepatocytes in vitro. Biochim Biophys Acta 2007;1770(4):659-65.
48. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch Biochem Biophys 1989;274(2):532-8.
49. Srinivasan M, Devipriya N, Kalpana K, Menon VP. Lycopene: an antioxidant and radioprotector against γ-radiation-induced cellular damages in cultured human lymphocytes. Toxicology 2009;262(1):43-9.
50. Çavuşoğlu K, Yalçın E. Radioprotective effect of lycopene on chromosomal aberrations (CAs) induced by gamma radiation in human lymphocytes. J Environ Biol 2009;30(1):113-7.
51. Lapenna D, De Gioia S, Mezzetti A, Grossi L, Festi D, Marzio L, et al. H2-receptor antagonists are scavengers of oxygen radicals. Eur J Clin Invest 1994;24(7):476-81.
52. Gifford R. Cimetidine induced augmentation of cell mediated cytotoxicity following in vitro and in vivo treatment. Fed, Pro 1983;39:924.
53. Mozdarani H, Khoshbin-Khoshnazar AR. In vivo protection by cimetidine against fast neutron-induced micronuclei in mouse bone marrow cells. Cancer Lett 1998;124(1):65-71.
54. Mozdarani H, Nasirian B, Haeri A. In vivo γ-rays induced initial DNA damage and the effect of famotidine in mouse leukocytes as assayed by the alkaline comet assay. J Radiat Res 2007;48(2):129-34.

55. Mozdarani H, Salimi M, Froughizadeh M. Effect of cimetidine and famotidine on survival of lethally gamma irradiated mice. Iran J Radiat Res 2008;5(4):187-94.
56. Razzaghdoust A, Mozdarani H, Mofid B. Famotidine as a radioprotector for rectal mucosa in prostate cancer patients treated with radiotherapy. Strahlenther Onkol 2014;190(8):739-44.
57. Davidson D. Secncy TR: Biological character ization of some improved rndioprotcclors. ln: Brady LW (cd). Radiation Sensitizers; Thcir Use in the Clinical Management of Cancer. New York: Masson; 1980.
58. Brizel D, Wasserman T, Strnad V, Wannemacher M, Henke M, Monnier A, et al. 6 Final report of a phase III randomized trial of amifostine as a radioprotectant in head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45(3):147-8.
59. Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, Monnier A, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000;18(19):3339-45.