NEW RADIOPROTECTANTS

TODAY AND FUTURE

Huriye Şenay Kızıltan

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Kızıltan HŞ,

Bezmialem Foundation University Medical Faculty, Department of Radiation Oncology, 2013, Istanbul, Turkey

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PREFACE

Radioprotectants have been investigated for a long time. An ideal radioprotectant has not yet been found. There is a great deal of research on the different radioprotectants used in different areas. With this book aimed to achieve a more accurate result by collating these publications.

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RADİOPROTECTANTS

Radiotherapy is generally applied as local treatment. By applying whole body radiotherapies it is also possible to get systematical results as chemotherapy, but these kinds of applications are restricted as they have many side-effects (Figure 1).

The chemical substances which reduce the side effects of radiotherapy are called radioprotectants. Radioprotectants have been investigated for a long time. An ideal radioprotectant has not yet been found. Publications on this subject are generally very narrow-scoped. There are some enzymes which render radiotherapy related free radicals harmless. Different radioprotectants are used according to the different cancer areas. There is a great deal of research on the different radioprotectants used in different areas. With this book aimed to achieve a more accurate result by collating these publications.

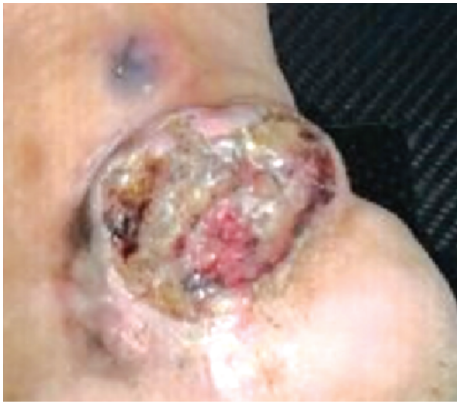

Figure 1: An ulcerovegetant skin tumor before radiation

Generally good responses are obtained from patients who are applied chemotherapy and radiotherapy (Figure 2,3).

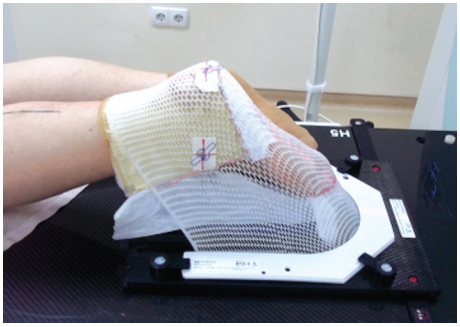

Figure 2: Radiotherapy masc for leg immobilization

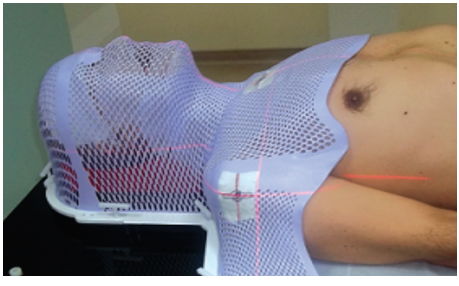

Figure 3: Head and neck mask

But the side effects are so varying that the immune system is weakened over time and the illness progresses. In cancers such as Hodgkin lymphoma, seminoma, choriocarcinoma, multipl myeloma, retinoblastoma and wilms, low dosage of chemotherapy and radiotherapy are sufficient. Therefore, not many side effects are seen. (Figure 4)

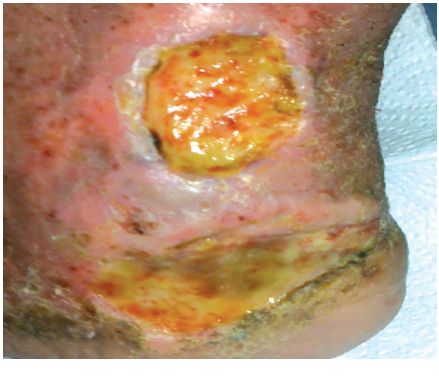

Figure 4: Radiation related necrose and skin burns (While goog result).

While new radiation thecnics, radiation related necroses and skin burns someties creates serious results (Figure 5).

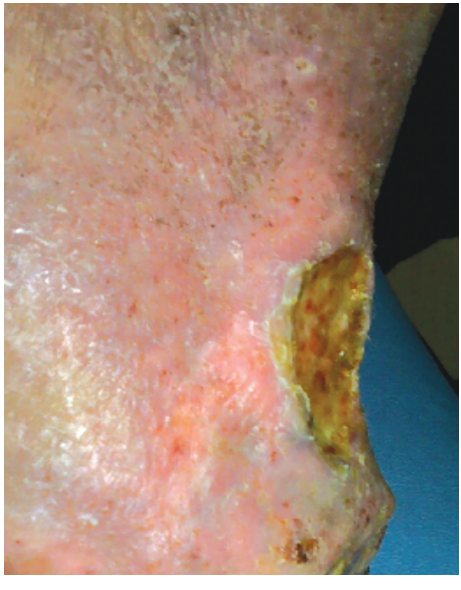

Figure 5: Radiation necrose and skin burns

Treatment results are also better. But for resistant cancers like bone, brain, soft tissue cancers, higher dosages are needed. And in the patients who are applied high dosages, the side effects overshadow the effect of the treatment.The basic aim in radiotherapy is the cancer cells and tissue. Different radiotherapy technics should be used on the principle that cancerous tissues are treated while the least amount of normal tissues is damaged (Figure 6.7).

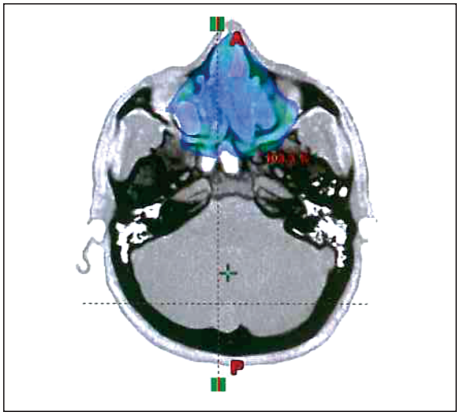

Figure 6: Intensive Modulation Radiation Treatment (IMRT) (An Advanced Radiotherapy technic)

Intensive Modulation Radiation Treatment (IMRT) generally reduces the side effects of radiation.

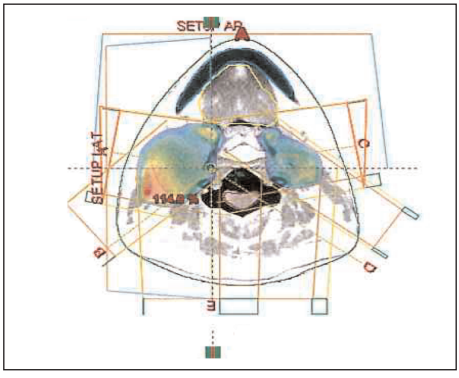

Figure 7: Radiation planning

Extra strong free radicals are formed during the radiotherapy (Kızıltan H 2010). These radicals kill the cancerous cells, yet also kill normal cells nearby. If these radicals did not exist, radiotherapy would be of no use. There are some enzymes which render these radicals harmless. For example, Superoxide dismutase renders superoxide radical harmless. The catalase enzyme reduces the formation of hydroxyl radicals and turns the peroxide radical into water. The glutathione peroxidase enzyme provides water formation from reduced glutathione.

A good radioprotectant must be cheap, it should not reduce radiotherapy effectiveness while protecting the normal tissues, in fact it should be able to increase radiotherapy effectiveness, with minor or no side effects. To this aim, the most well-known and commonly used radioprotectants are sulphuric compounds. Sulphuric compounds have a good radioprotectant effect (Brizel DM et al 2000). However, despite reducing the effectiveness of the tumor tissue while protecting against radiation, they are expensive and have many side effects which restrict their usage. Nevertheless, today sulphurous medicines which contain thyliol are used as radioprotectors. As a result of radiobiological research, compounds which contain sulphydryl (SH) are found to be strong radioprotectants.

Cysteamine, cystamine, thiol compound and ethiol, which are among the sulphurous compounds that have been the subject of the research, are compounds which are toxic for the body, so their usage is restricted. The toxic effect of ethiol is relatively lower. When it is applied through the vein, there is the risk of causing hypotension. When applied subcutaneously, however, this effect decreases. ethiol and its active metabolite WR-1065 decrease the cell life related to radiotherapy. It could also prevent the formation of secondary cancers by decreasing the mutagenesis resulting from radiotherapy (List AF et al 1999).

WR 1065, which is an active form of **ethiol**, shows its effect by increasing the dismutase enzyme. In research conducted by Murley JS et al, the radioprotector effect of Superoxide dismutase enzyme was investigated. After applying a chemical substance that increases the Superoxide enzyme in RKO36 to human subjects and mice, radiotherapy was applied and it was stated that a radiation protective effect was obtained. In this research, WR-1065 and TNF Alfa were used to increase the antioxidant enzymes in the plasma. Superoxide dismutase, aka mangan superoxide dismutase, can raise the enzyme level 15 times and its activity 5.5-6.9 times. The SOD level reaches a maximum in 24 hours with

WR-1065 treatment. In this process, the catalase and glutathion peroxidase (GPX) enzymes are also monitorized. While the Catalase level only increases 2.6 times with WR-1065 treatment, no change is seen in the glutathion peroxidase level. It was seen that the radioprotectant effect rises to the maximum level when the SOD rises to the maximum level with WR-1065, i.e. Thiol treatment. Thus, the RKO36 cells to which radiotherapy was applied radiotherapy were harmed less with the rise of the radioprotector effect and also, their life span rates increased (Gosselin et al 2002, Brizel DM 2000).

In research carried out by Jens B et al with 815 patients who had head and neck cancer and who were applied radiochemotherapy. The patients were tracked for 2.3-149 months after the treatment. While significant changes in xerostomia, the sense of taste symptoms which are seen among late complications, were observed with the effect of amifostine, no diminution was observed in interstitial lymphedema complication (List AF et al 1999).

The sulphurous compounds **L-Carnitene, alpha lipoic acid** are good radioprotectants as they increase the glutathion level (Saly SA et al 2010). Furthermore, their side effects are very low and they are beneficial for the body in certain dosages.

Vitamin E (Kumar KS et al 2002)**, Vitamin C** (Gupta A et al 2010, Dani M et al 2007), are also radioprotectant effective (Figure 8).

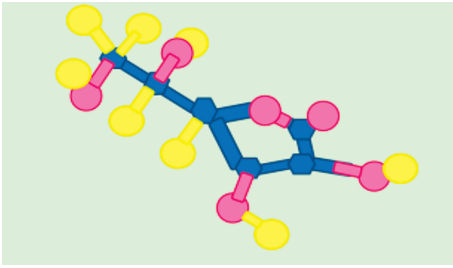

Figure 8: Vitamin C shematic image

In particular, when they are given in their natural state, they diminish the bone marrow toxicity, oral mucositis. Vitamin E and C reduce radiation related mutation and cell death. In research conducted on patients with head and neck squamous cell carcinoma, all patients were administered chemotherapy and concurrent radiotherapy. During the radiotherapy, all patients were tracked and closely in terms of tumor response and side effects. The side effects were assessed according to RTOG toxicity criteria (Cox JD et al 1995). And the clinical response rates were defined in accordance with WHO criteria. In the blood examples before and after the radiotherapy of the group in which full response was obtained, it was shown that **ascorbic acid** is significantly high

when compared to the patients in the other group ($p>0.05$). But no significant change could be shown in the thiol levels. The redox system in a cancerous tissue was harmed. Therefore, it can be deduced that cells are extra vulnerable against oxidative damage.In a research done by Kumar KS et al it was stated that especially when they gave Vitamin E sc, although Co60 was applied at the lethal dosage level, they obtained a significant radio-protectant effect in the radiotherapies made with 400IU/kg Vitamin E application on CD2F1 model male mice (Kumar KS et al 2002).

Green tea: In a Japanese study, when mice exposed to lethal x rays were then given epi-gallocatechin (EGCG), which is one of the green tea polyphenols in the water, it was detected that their life spans rose significantly (Guo S et al 2010). (Figure 9)

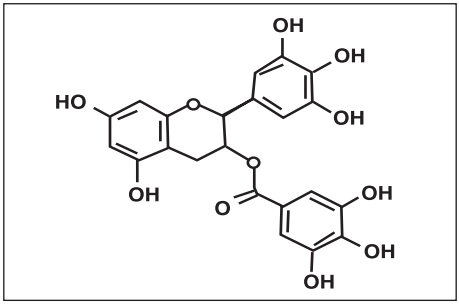

Figure 9: Epigallocatechine shematik illus-tration

Glutamine: In research by the Department of Surgery, McGill University, Montreal, Quebec, Canada, the effect of glutamine added to the hydrolisate based elementary diet on the dogs which were administered treatment for the purpose of pelvic therapy was investigated. In both diets, a significant radioprotection against the damage of radiation was detected. With histological and electron microscopical research, it was shown that tissue damage decreased in both diets. Alongside this, in only the elemental diet group it was observed that after radiotherapy, the antioxidants like xanthine oxidase, superoxide dismutase were significantly more ($p<0.002$). It was decided that the obtained good results bound to the increase of other chemicals as dismutase rather than glutamine (Mc Ardel AH et al 1994).

Propolis, which is among the radioprotectants which have yet not been investigated to a sufficient degree but found worthy of investigation, showed that cafeic and phenetyl esters, which are among the most important active substances in it, can reduce the side effects of radiotherapy and chemotherapy (Gremy O et al 2010, Vesna B 2009). Propolis is beneficial in skin burns resulting from radiation, defluxions and myocardial damages resulting from chemotherapy. It increases the red blood cells

at the rate of 25-30% and haemoglobin at 15%. (Figure 10)

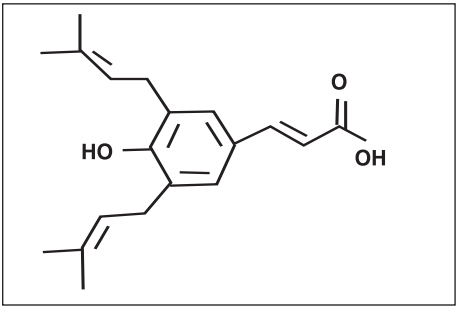

Figure 10: Chemical structure of Propolis

When **Oleuropein** (Figure 11), which is another chemical substance, is administered with the radiation generated from X-rays, it prevents the chromosome damage resulting from radiation (Garcia O et al 2002).

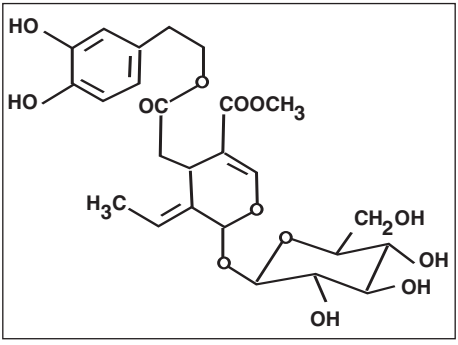

Figure 11: Chemical structure of Oleuropein

Pollen has a protective effect against X-rays (Wang et al 1984, Dani M 2007) (Figure 12). Rutin, dimethylsulphoxide i.e. DMSO and diosmine are other radioprotectants which require further research.

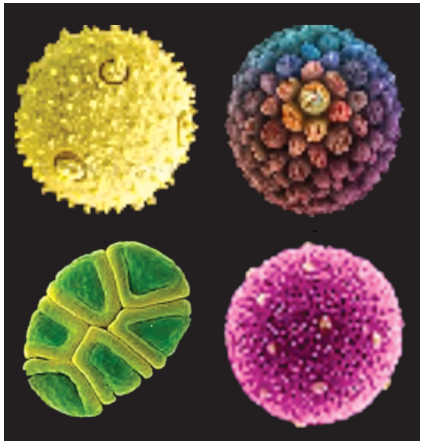

Figure 12: Different Pollen spices

In skin reactions resulting from radiation

Most of the research done to reduce skin reactions was mostly preformed on patients with breast cancer; results are not very homogenous but do offer important ideas (Asbeck F et al 1958, Boström A et al 2001). While the skin reactions were investigated in these studies, the RTOG acute skin reaction score system was used the most. According to RTOG

Scorring system:Grade I skin reaction is only skin eritem (Figure13, 14).

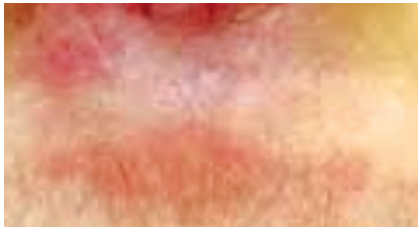

Figure 13: Grade I skin reaction (Erytem)

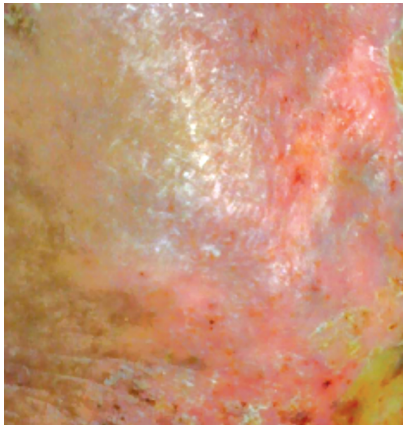

Figure 14: Radiotherapy related Grade II skin reaction (Skin desquamation)

Grade III skin reaction is skin necrosis (Figure 15)

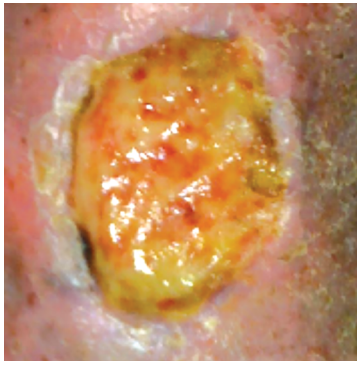

Figure 15: Grade III skin reaction

Topical steroid applications in skin reactions resulting from radiotherapy: When the research done on this subject was investigated, it was seen that nearly all of them have different features. Only one of them (Bostrom A et al 2001), 0.1% mometasone furoate applications - provided significantly good results. No difference was observed between methylprednisolone and beclomethasone applications and placebo.

Washing applications: In three moderate-sized randomized studies, the effect of washing the skin or areas with hair while the radiotherapy continued was investigated (Roy I et al 2001, Olsen DI et al 2001, West bury C et al 2000). In these studies it was shown that the skin reactions reduce with washing. A total of 48% of

the patients used soap in washing and 18% of them washed only with water. The other patients did not use a definite method.

Sucralfate or sucralfate products: Three separate randomized studies were done on patients with head neck cancer. Sucralfate topical was used on some of the patients while some were used orally, and results were compared with a placebo. While Wells M et al 2004 observed a significant reduction in wet desquamation with sucralfate cream, Evensen JF et al 2001 showed that there is a decrease in the placebo group on the average desquamation score with placebo cream. Evensen and Wells used different products of sucralfate in their studies (Wells M et al 2004, Evensen JF et al 2001).

Topical Water based enzyms: The effect of different water and enzym cream on radiotherapy skin reactions was investigated in research (Fenig E et al 2001). Fisher J et al 2000 used Aloe Vera on 34% of the patients as a support product, other products on 19% of them, and used no product on the rest. In this research, no difference was observed in terms of skin reaction.

Oral enzymes: The groups with head and neck cancer who were administered oral hydrolytic enzymes and who were not during radiotherapy were compared (Gujral MS et al

2001, Dale PS 2001). In two studies, it was shown that enzyme treatment is beneficial. The observing rate of grade 2 or more skin reactions is significantly lower in the enzyme group. While in the group which was administered enzyme in the sixth week of radiotherapy 28% reactions were observed, in the control group, which was not administered enzyme, 88% of grade 2 or more skin reactions were observed. While in the control group, in the sixth week 4%, in the seventh week 20%, in the eight week 40% grade 4 skin reactions were observed, none of the patients of the enzyme group showed skin reactions above grade 3. In the pathological research done as pre and postradiotherapic, the enzyme group scores were found to be significantly better.

Ethiol: Ethiol is a thiol product that protects tissues against cytotoxic effects resulting from radiotherapy and chemotherapy (Dunst J et al 2000, Kouvaris J et al 2002). In a small study on patients who were receiving radiochemotherapy, the groups who were administered intravenous ethiol and those who were not were compared. In the ethiol group, a significant decrease in the rate of erythema and skin reactions above grade 2 were observed ($p=0.003$). While the grade 2 skin reaction rate was 7% in the ethiol group, in the control group it was

53%. In both groups, grade 3-4 reactions were not observed.

Topical acid cream: In groups which were applied hyaluronic acid cream, a significant success was achieved (Primavera G et al 2006, Ulana K et al 2001).

Aloe Vera: Three important studies were done with Aloe Vera in order to prevent skin reactions resulting from radiotherapy (Heggie S et al 2002, Leonardi MC et al 2008, Schmut M et al 2001), two of which were large-scale and performed blind, and the radiotherapy dosages used varied greatly. Less radiation skin reactions than expected were detected. Williams also published a non-blind study in which he compared the Aloe Vera and the control group. No significant difference between them was observed. But in Heggie's research, a significant advantage with Aloe Vera was observed. When it is assessed cumulatively, the reactions are less when compared to the control group ($p<0.001$).

Chamomile cream: In a study by Maiche et al, chamomile cream and almond ointment were compared (Maiche AG et al 1991). Less reactions were observed in the chamomile group but the results were not found to be significant. In a double blind controlled study done on 48 women, patients who were administered chamomile cream and almond oil on the radio-

therapy area were compared. No difference between them was found. But the patients preferred chamomile oil as it absorbed quickly.

Dressing: In many studies done using dressing, different results were obtained. In a comparative research, a group of patients administered protective treatment whose skin was covered with polymer adhesive skin sealant (PASS) and a group which was not administered anything were compared. In another study conducted on 54 people, while in the group administered PASS, only one patient's radiotherapy had to be suspended in the control group 24% of treatment cases were suspended. In research by Mac Millian et al 2007, two groups who were applied wet dressing using hydrogel and dry dressing were compared . It was detected that the skin reactions were seen less with wet dressing (p=0.03). In Mak SS et al's 2007 research, hydrocolloid dressing and gentian violet were compared. Gentian violet gave better results.

Agents and chemicals which are protective against radiation pheumonitis

Radiation pneumonitis generally occurs 6-8 weeks after radiotherapy. Complaints such as cough, dyspnea, chest pain can be seen. (Figure 16)

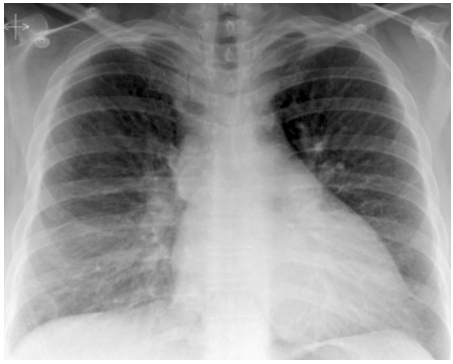

Figure 16: Radiation Pneumonia

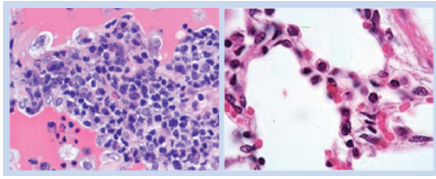

Figure 17: Histopathologic images of Radiation Pneumonia and normal lung

Corticosteroids are mostly used in its treatment. A very rare element cerium oxide, which is known as a free radical hunter, was investigated for protection qualities against radiation pneumonitis. The protector effects of cerium oxide against high dosages of radiation on murine models was investigated nanotechnologically. It was seen that cerium oxide nanoparticles were tolerated well by the ani-

mals. It was reported that the radiation pneumonitis is very low when given with high dosages of radiotherapy. This research was a big step in radiation protection (Luis H et al 2008). In another rat study done with manganese superoxide dismutase, the C57BL/6J rats were intrathecally injected manganese superoxide dismutase plasmide liposome complex (MnSOD), metallothionein, LacZ-pl and 24 hour later, the thorax cavity was administered radiotherapy. A significant increase in their life span was observed when compared to the group which was not applied MnSOD. Another group was injected with the same pharmaceutics intraesophageally. When compared to the group which was not administered MnSOD, a significant life advantage was obtained in this group, too (Michael W et al 2002). No positive result was obtained from more comprehensive research done using converting enzyme inhibitors, which showed that they are protective against radiation pneumonitis in some smaller studies (Wang LW et al 2000).

Oral Mucositis Resulting From Radiation:

This is an acute radiation side effect which generally occurs in the second to third week of radiotherapy (Figure 18, 19, 20).

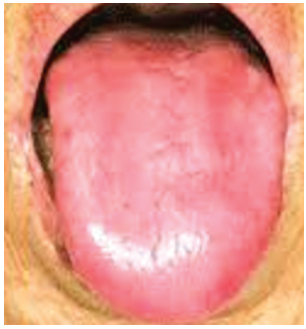

Figure 18: Radiation related Grade I oral mucosyitis

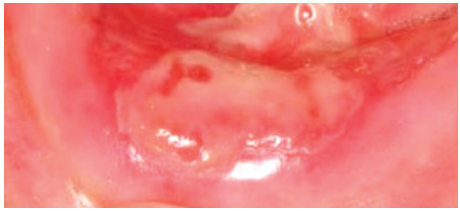

Figure 19: Radiation related Grade II oral mucosyitis

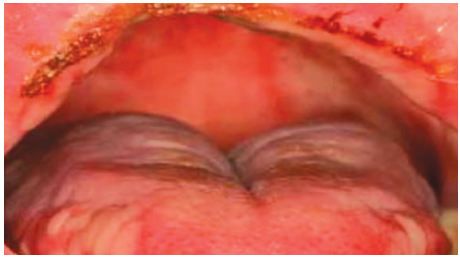

Figure 20: Radiation related Grade III oral mucosyitis

Oral mucositis intensifies with the effect of the pathogens, which secondarily settles to the mucosal damage resulting from radiotherapy and the neutropenia which is formed. The effect would increase even more if chemotherapy was also applied. The importance of diet in the protection against oral mucositis is great (Colasento JM et al 2005), and fungal and viral infections accompany them the most frequently. Antifungals such as nystatin are used the most to treat mucositis (Wolfgang J et al 2001), and good results were obtained in the studies done with manganese superoxide dismutase (Dorr W et al 2007).

Mouth hygiene: This is the most effective way to protect against mucositis. Simple preventions such as regular mouthwash and brushing the teeth are very important in mucositis prophylaxis (Wolfgang J et al 2001).

Glutamine: Glutamine is the most important energy source in the mucosal cells. It helps the repair of the epithelium cells (Figure). In research conducted by Matthew K et al, prophylactic glutamine treatment was investigated. Seventeen patients with head and neck cancer were separated in a randomized way, and those who were given 2g glutamine during the radiotherapy and those who were not were compared. Less mucositis were seen

in those who were given glutamine (Huang EY et al 2000). In the group which glutamine was administered, less oral mucositis was observed and grade 3 reaction decreased significantly (p=0.0168).

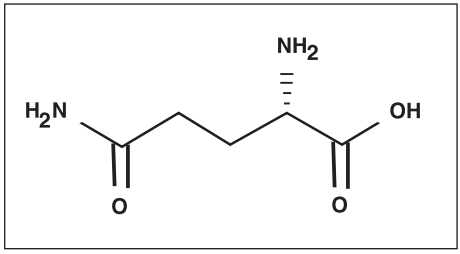

Figure 21: Chemical structure of Glutamine

Chamomile: Chamomile extract has an inhibitor and antimicrobial effect on cyclooxygenase, lipoxygenase, prostaglandins and leukotrienes, in vitro (Berry M et al 1983, Aggag ME et al 1972, Linc LC et al 2006). It increases the cortisone swing by stimulating the pituitary glands and adrenal glands with the effect of the azulens and this reduces the histamine secretion. In research on 98 patients, the mouthwash form of Kamillosan liquidum, which is obtained from German Chamomile, was applied as 15 drops three times a day on patients who were receiving radiotherapy and chemotherapy. The patients were separated

into two groups: 66 radiotherapy and chemotherapy patients were given the treatment as a protectant and for 32 patients, who were administered chemotherapy alone, this treatment was applied after the mucositis occurred. Among 20 patients who were administered radiotherapy, only in one, and in the last week of treatment, did grade 3 mucoistis occur. In 65% of patients, intermediate grade mucositis, and in 30% low grade mucositis developed. Among 46 patients who received chemotherapy and radiotherapy simultaneously, in 36 of them mucositis was not observed. In all 32 patients who are not applied prophylactically chamomile mouthwash and receive chemotherapy was observed. With the treatment, the mucositis symptoms in all patients ceased in seven days (Carl W et al 1991).

Pure honey: Biswa Mohan et al 2008 and colleagues made a preliminary study in this subject. Radiotherapy which included head and neck cancer and oropharyngeal mucosa and 40 patients were observed. They were given 20 ml pure honey 15 minutes prior to, 15 minutes after, and six hours after the radiotherapy. These patients were assessed each week in terms of oral mucositis. They were graded using the Radiation Therapy Oncology Group grade system. While in the group given pure honey with the radiotherapy, 20% oral

mucositis was observed, in the group which was not given pure honey, 75% oral mucositis was observed (p 0.00058). While in the group which is treated with honey, no weight loss was observed, in the other group, 55% weight loss was observed. It was stated that topical pure honey reduces oral mucositis dramatically, is an advantage in that it is cheap, but multicenter research is still needed (Biswa Mohan et al 2008).

Zinc: In a small study done on patients with head and neck cancer it was stated that zinc given with radiotherapy reduced the mucositis rate at a medium level (Lin LC et al 2006).

Fibrosis and necrosis resulting from radiation

This is one of the late reactions resulting from radiation and nearly always permanent (Figure 22, 23).

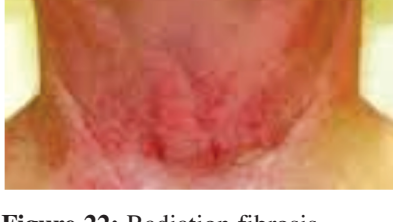

Figure 22: Radiation fibrosis

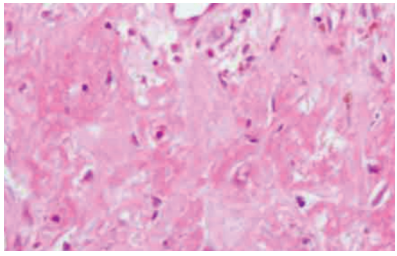

Figure 23: Radiation fibrosis histopathologic image

The local and general stimulant factors need to be eliminated in order to effect protection. Different methods include anti-inflammatory treatmnt with corticosteroid and interferon, circulation accelerator treatment with pentoxipyllin, again hyperbaric oxygen treatment, and antioxidant treatment. The most frequently used are the applications of pentoxipyllin along with vitamin E (Audrey J L et al 2005, Aygenc E et al 2004).

Green tea: In the research of Beijing Tongren Hospital in China, green tea polyphenols protection against radiotherapy in rats was investigated. A group of rats was given green tea and the other was placebo 14 days before the radiotherapy. Then a single dose of 15 Gy was applied to the head and neck area. In the third, sixth and 30th days after radiotherapy, the submandibular gland was excised

with autopsy. It was seen that cell damage resulting from radiotherapy was significantly low in the group given tea polyphenols (Peng Z et al 2011).

Haematologic toxicity

Haematologic toxicity related to radiotherapy may crate also low dose radiation (Figure 24, 25).

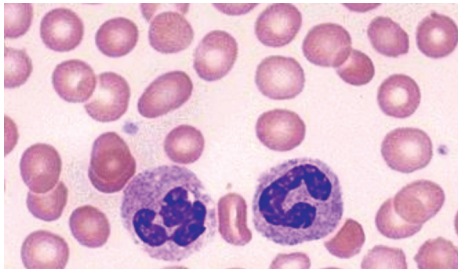

Figure 24: Normal blood cells histopathologic image

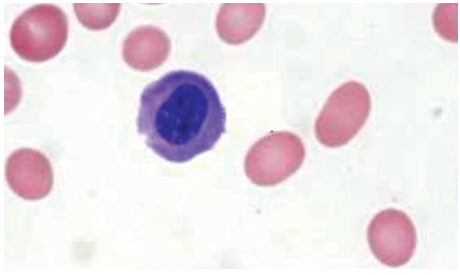

Figure 25: Anemic blood cells

Before the green tea research in China, radiotherapy was applied to the whole body, then green tea polyphenols containing 50% epigallocatechin was given. The highest radioprotector effect was observed in 50% concentration, which was found to be most effective as a radioprotector for the spleen, erythrocytes, leucocytes, and thrombocytes. Superoxide dismutase, malonyl aldehyd activities increased the antioxidant capacity (Guo S et al 2010). Bone marrow protective effects were obtained with substances such as thymoquinone, caper and pollen. New research on these subjects is needed (Figure 26).

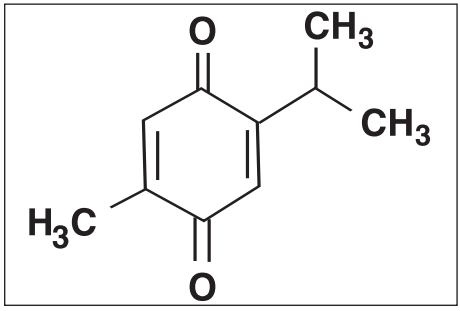

Figure 26: Thymoquinone, chemical formula

Hepatotoxicity related to radiation

The liver is very sensitive to radiation. Venooclusive disease and icterus are very

often evidence particularly high radiation doses eventually during radiotherapy or postradiotherapic sessions (Figure 27, 28).

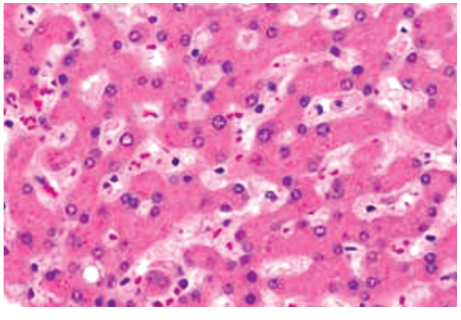

Figure 27: Normal human liver, histologic image

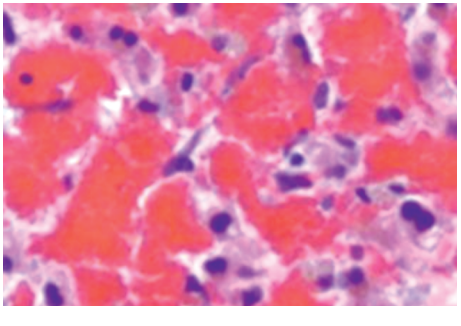

Figure 28: Hepatotoxicity, human liver, histopathologic image

Ascorbic acid monoglucoside (AsAG ascorbic acid's glucose derivation). It protects rat liver against radiation, in vitro. Dani

M et al in their study demonstrated that it has a protective effect against 25Gy gamma radiation. It shows this effect by preventing lipid peroxidase damage. The whole body was administered AsAG before 4Gy gamma radiation. A significant decrease in liver toxicity was informed (Dani M et al 2007).

L-Carnitene and Alpha Lipoic acid: In research by Sally SA et al, the radioprotective effect of L-Carnitene and Alpha Lipoic acid was investigated (Sally SA et al 2010). It was shown that in rats, the bone marrow and liver damage related to radiation could be reduced with L-Carnitene and Alpha Lipoic acid treatment. In rats, whole body radiotherapy in single doses of 6Gy was administered every day, and then 300mg/kg L-Carnitene and 150mg Alpha Lipoic acid treatment was applied over 10 days. Normally, with gamma radiation's effect, a significant decrease is seen in bone marrow and the liver, and Superoxide Dismutase and Glutathion Peroxidase enzymes, and this increases the lethal effect of radiation on cells. But in this research, it was shown that when radiotherapy, L-Cartinine and Alpha Lipoic Acid treatment are given together, as the Superoxide Dismutase and Glutation Peroxidase enzyme levels do not drop below the normal value, the cells are protected against radiation.

Silymarin In research by Ramadan LA et al, in a group of patients who were administered 3-6Gy full body radiotherapy, after 70mg/kg(-1) silymarin was given to patients in oral, single or fractionated dosages, IV 50mg/kg (-1), a significant decrease in the hepatotoxicity rates, when compared to the patients who were not applied silymarin (Figure 29), was observed (Ramadan LA et al 2002).

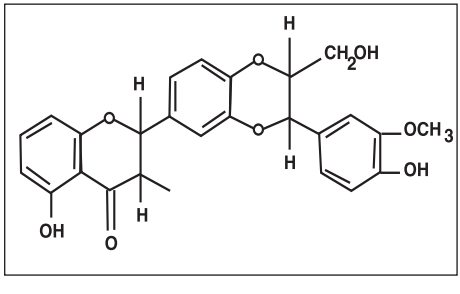

Figure 29: Slyimarine chemical formula

The liver cell protective effects of thymoquinone and N Acetyl Cysteine is known. There is a need for research in these subjects as well.

Diarrhea resulting from radiation

Proteolytic enzymes: Radiotherapy applied to the pelvic area may cause nausea, vomiting and diarrhea (Figure 30).

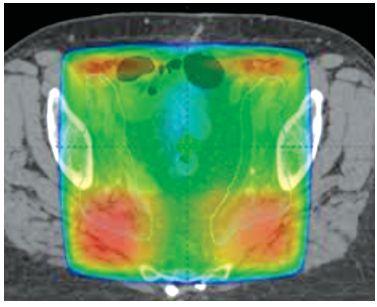

Figure 30: Pelvic radiotherapy

In a double-blind placebo controlled research of 56 patients, the proteolytic enzymes were given along with radiotherapy, but no side effect reducing effect was detected (Guo S et al 2010).

Probiotics: In one study by Urbancsek et al, in patients who were given Antibiophilus along with radiotherapy, no decrease in the rate of diarrhea was detected (Urbancsek H et al 2001, Martin T et al 2002).

Green tea: In research done in South Korea, the different types of catechin in green tea and green tea non-decomposed full extract were compared. After radiotherapy with gamma rays, the liveliness of jejunal crypts, endogenous spleen colony formation, the death of jejunal crypt cells or apoptosis were investigated. It was announced that the green

tea extract obtained from the whole green tea is more effective in radioprotection (Guo S et al 2010, Lee HJ et al 2008).

Studies done on the esophagitis with amifostine (Brizel DM et al 2000, Jens B et al 2007), superoxide dismutase (Michael W et al 2002) and yielded good results. Research was also done with nephrotoxicity amifostine (Grdina, D. J et al 2000, Gosselin, T. K et al 2000).

In cardiotoxicity prophylaxis, research done with thymoquinone and bromelain is promising. Wider and more homogenous research is needed. That the effects of colony stimulate agents in the treatment of myelotoxicity and hematologic toxicity is proven and widely used is not stated here.

Radioprotectants have been extensively investigated over a long period of time, yet, an ideal radioprotectant has not been found. Existing literature on this subject is generally very narrow in scope. Sulphuric compounds are good radioprotectants (Kızıltan HŞ 2010, Brizel DM et al 2000), but reduce the effect of radiotherapy on tumorous tissue while protecting against radiation, are expensive, and have a lot of side effects restricting their usage. Research on this subject, conducted on patients with head and neck cancer, is very striking (Gupta A

et al 2010). In this research it was stated that in the group which was administered radiotherapy and obtained a full response, the **ascorbic acid** level in blood samples before and after the radiotherapy were significantly higher than the patients of the other group, but there was no significant change in thiol levels. The redox system was damaged in a cancerous tissue. So the cells were extra vulnerable against oxidative damage (Barry H 2007). For this reason it is very important to reduce this oxidative damage. Ascorbic acid needs to be further researched as a radioprotectant because of its oxidative damage reducing effect. In many publications, the cytotoxic effect of ascorbic acid against cancerous cells was shown (Salomi MJ et al 1991, Enomoto S et al 2001). As it was stated before, an ideal radioprotectant should not protect the cancer cells while protecting the normal cells, and it must even be able to kill them. Further, it should be cheap, easily accessible, and easy to apply. Ascorbic acid seems to be a broad spectrum agent including all these features within itself. The other broad spectrum agents which include these features but for which sufficient research has not been carried out include thymoquinone (El-Kadi A et al 1986, Salomi MJ et al 1991, Enomoto S et al 2001) and sulforaphen.

In **green tea** research (Guo S et al 2010, Lee HJ et al 2008), it was stated that the extract obtained from whole Green tea is more effective in radioprotection. Like this, It was stated that topical pure honey (Biswa M et al 2010) reduces oral mucositis dramatically, is an advantage in that it is cheap, but multicenter research is still needed. The radioprotectant effects of substances like cafeic and phenetyl esters, which are among the most important active substance in propolis, Oleuropein and Pollen were demonstrated (Gremy O et al 2010, Vesna B 2009, Garcia O et al 2002, Wang et al 1984, Dani M 2007), but broader and more homogenous research needed in these subjects.

The previous assumption that washing (Roy I et al wash 2001) while radiotherapy is ongoing will increase skin reactions has now been completely revised. In contrast, it was accepted that skin reactions increase with sweating and infections formed in the loops, and washing is very beneficial. It was observed that using or not using soap during washing does not affect the result. It was reported that the radiation pneumonitis rate is very low when cerium oxide (Luis H et al 2008) nanoparticles are administered with radiation. This research was a big step in protecting against radiation pneumonitis. It was observed that the importance

of nutrition (Carl W et al 1991) is great in the protection against oral mucositis, and in this, pure honey is very effective. Such a method that patients could use easily could be a big advantage, rather than using expensive agents. The same agents need to be investigated in the protection against esophagitis. The radioprotective effect of L-Carnitene and Alpha Lipoic acid (Sally SA 2010) was shown, but as the hepatoprotectant effects of agents such as thymoquinone and acetylsisteine, for which research with radiotherapy is not sufficient, are also known, they must be researched in terms of liver protection against radiotherapy, too. Rutin, dimethyl sulfoxide i.e. DMSO and Diosmin, glucoraphanine and sulphoraphen are the radioprotectants which require further research. As it is also shown in pure honey and green tea research, using non-decomposed pure substances rather than decomposed chemicals may be able to increase the success of future research in this subject.

The radioprotectant effect of compounds which contain thiol has been proved, but as they have a lot of side effects, are expensive, and are difficult to apply, their use is restricted. It will be very beneficial if the orally applicable forms of agents and products like Sulforaphan, ascorbic acid, glucoraphanin thymoquinone, garlic, cabbage, broccoli,

pollen, propolis are investigated as radioprotectants (Kızıltan HŞ, Gupta A et al 2010, Gremy O et al 2006, Vesna B et al 2009, Benaventa et al 2002, Asbeck F et al 1958, El-Kadi A et al 1986, Salomi MJ et al 1991, Enomoto S et al 2001, Kathleen A et al 1998, Ulana K et al 2011, Kim. S.J et al 2005). Research on these subjects is, unfortunately, not homogenous or broad in scope. There is a huge need for wider, homogenous and randomized research.

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