Ionizing radiation induced skin damage: Mechanism, prevention and therapy

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Ionizing radiation leads to biological responses in the organism through physical and chemical phases. One of the most frequently damaged tissues is the skin. Radiation induced acute skin symptoms are mainly dose dependent, can vary from mild erythema through severe dermatitis to extent necrosis. Late effects of radiation such as malignant tumors, chronic skin ulcers put heavy weight on the patient and doctor as well. These damages can be prevented or decreased by the use of radioprotective agents, which lightens the evolving symptoms, reduces the permanent damage and last, but not least decreases the costs of medical treatment.

Introduction

The mechanism by which radiation causes damage to human tissue is the ionization of atoms in the material (physical phase). During radiation, the energy absorbed by the orbiting electrons of irradiated matters leads to the excited state of the molecule. Photons having at least 10–12 eV energy are able to evolve ionizations (ionizing potential).

In the next, chemical phase the critical molecule is damaged directly or indirectly. During direct action the ionizing radiation interacts with the critical biological molecule itself. In case of indirect action free radicals, mainly highly reactive aqueous ones (·OH, ·O₂H, H₂O₂, H, O₂−) act as intermediaries in the transfer of radiation energy to biological molecules.

In biological aspect the processes affecting the cell membrane and the DNA are of high priority. Due to the interaction with free radicals lipidperoxidation begins in the lipid layer of cell membranes leading to severe structural defects. The three major types of DNA damages that ionization can produce are base damage, single and double strand breaks. At this stage repair mechanisms, such as excision repair, postreplication repair or repair of double strands breaks can prevent further damage.1,2

All these processes result in wide range of biological effects (biological phase). The structural damage of membranes leads to enhanced permeability, enzyme defects, cell death. If the repair function was not capable of coping with the DNA damage it would lead to functional disorder, cell death or malignant transformation.

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The extent of biological damage depends on the dose of radiation, the dose rate, the type of radiation and the attributions of affected tissue. The radiation sensitivity of a tissue is proportional to the rate of cell proliferation and inversely proportional to the degree of cell differentiation. For these reasons one of the most sensitive tissues is the skin.

Discussion

Cell level effects of radiation on skin

The sensitivity of distinct epidermal cells to radiation is diverse. The basal and follicular cells are the most sensible, while the connective tissue and the sweet glands are relatively resistant.
**Epidermis:**
Although low doses of radiation (D$_0$: 0.7–0.9 Gy) lead to epidermal cell death, the majority of basal cells survive and total regeneration occurs in 2–3 weeks. With relatively large doses of radiation such as 10 Gy or more, the number of basal cells diminishes below 20%, so the basal layer can not prohibit the intercellular liquid influx. This process conducts to blister formation, then rupture resulting moist desquamation (scaling). Limited regeneration also occurs, but the less basal cell can only produce thinner epidermis. Extreme doses of radiation (>50 Gy) cause the extinction of basal cells and regeneration can not occur.1,3

**Hair follicles:**
Due to ionizing radiation hair dysplasia (thinning) and epilation (loss of hair) occur. Between 0.5–5 Gy the degree of dysplasia shows linear dose correlation, so the dose of radiation can be predicted. Epilation commence with 3–4 Gy in about 3 weeks after radiation. Hair can return in 1 year, but with doses of 7 Gy or more the hair loss is permanent.1,3,4

**Vessels:**
Larger doses of radiation than 3 Gy lead to histamine deleration from histiocytes localized around the vessels. Histamine enhances the permeability of vessels generating 1–2 days lasting erythema and oedema. Endothelial cells of dermal and subcutaneous vessels are rather radiosensitive (D$_0$: 1.5 Gy). About 7–10 days after radiation their depletion is succeeded by an atypical proliferation resulting vessel obstruction and hypoxia. The hypoxia induced compensatory capillary dilatation responds for the later erythema (erythema proper) occurring 2–3 weeks after radiation. As a late consequence of 10 Gy or higher doses, vessel wall destruction and fibrosis develop causing circulation disorder, which leads to skin atrophy, or in severe cases to ulcer formation.3,4

**Sebaceous glands:**
Sebaceous glands are damaged by doses of more than 3 Gy resulting dry skin 25 days after radiation.3
Radiation induced skin symptoms

Radiation induced skin damages are classified into four groups according to the dose of radiation.

First degree radiation dermatitis occurs with lower doses than 10 Gy and clinically similar to the first grade burn injury. In a short time after irradiation pruritus might emerge, followed by erythema, epilation and dry desquamation in 2–3 weeks. After the acute period pigment disorder, usually hyperpigmentation can stay behind.

Second degree radiation dermatitis (10–20 Gy) resembles to second degree burn injuries. Shortly after the irradiation early, then late erythema occur in conjunction with pain. In 2–3 weeks, due to the severe damage of basal cells moist desquamation, then painful ulcer evolves. After the regeneration dry, mostly hyperpigmented, epilated and deliberately vulnerable skin develop.

Larger doses of radiation (>20 Gy) cause third degree radiation dermatitis with a clinical picture of 3rd degree burns. Immediately after the irradiation strong pain, erythema appear and after the rejection of the necrotized epidermis ulcer is left over. The tendency to regeneration is poor, mainly due to the harm microcirculation. In case of healing recidivation often occurs.
Table 2. Classification of skin symptoms depending on the dose of radiation
(Source: Modified from Ref. 4)

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose of irradiation</th>
<th>Symptoms</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st degree radiation dermatitis</td>
<td>≤10 Gy</td>
<td>prodroma- pruritus</td>
<td>minutes–hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>manifest- erythema, dry desquamation, epilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>subacute- erythema, pigmentary disorder</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chronic- erythema, epilation, teleangiectasia</td>
<td>6–9 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>late- angioma</td>
<td>undetermined</td>
</tr>
<tr>
<td></td>
<td>2 nd degree radiation dermatitis</td>
<td>prodroma- erythema</td>
<td>minutes–hours</td>
</tr>
<tr>
<td></td>
<td>10–20 Gy</td>
<td>manifest- blister formation, moist desquamation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>subacute- ulcer, vulnerable skin</td>
<td>6–9 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chronic- keratosis</td>
<td>undetermined</td>
</tr>
<tr>
<td></td>
<td></td>
<td>late- malignant tumors</td>
<td>6 months–years</td>
</tr>
<tr>
<td></td>
<td>3 rd degree radiation dermatitis</td>
<td>prodroma- erythema, pain</td>
<td>minutes–hours</td>
</tr>
<tr>
<td></td>
<td>&gt;20 Gy</td>
<td>manifest- necrosis, ulcer</td>
<td>days–3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subacute- ulcer</td>
<td>6–9 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chronic- ulcer</td>
<td>6 months–years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>late- ulcer</td>
<td>undetermined</td>
</tr>
<tr>
<td>Chronic stage</td>
<td>chronic, &gt;10 Gy total dose</td>
<td>skin atrophy, eczema, ulcer</td>
<td>undetermined</td>
</tr>
</tbody>
</table>

Chronic radiation dermatitis (type 4) occurs in case of permanent, minimum 10–20 Gy total doses of radiation. Xerosis, atrophy, poikiloderma, teleangiectases and epilation can be seen on the affected skin. Exulceration and malignant tumor formation are not rare. In the background of the symptoms combined cell depletion, vessel damage and fibrocyte dysfunction act together.2,3

Prevention of radiation dermatitis

In case of expectable radiation (e.g., radiotherapy), dermatitis can be prevented or decreased by the use of radioprotective agents. These compounds can be divided into the following groups according to their mechanism:4,5

Free radical scavengers form stable compounds with free radicals preventing their interaction with other biologically important cell components.

Hydrogen donators: Exposure to radiation can convert the R-H molecule into an R* radical. Protective agents can donate a hydrogen atom to this radical restoring it to its original state.

Mixed disulfide formation: Sulphydryl compounds of aminothiols form disulfide bonds with sulphydryl containing cellular proteins. During the interaction of these mixed disulfides with free radicals, in 50%, when the sulfur atom of vital protein is reduced and the protective agent is oxidized, the cellular protein is not damaged.

Delayed cell division: Sulphydryl compounds also act by reversibly binding to the DNA and prohibiting the replication, hence providing more time to repair processes.
Induction of hypoxia: Oxidation of thiol compounds consume huge amount of oxygen during radiation. The radioprotective effect of hypoxia is well known. Antioxidants neutralize the products of radiolysis and free radicals, inhibit the lipid peroxidation, and stabilize membrane structure.

For the prevention of radiation dermatitis mainly the antioxidants are used in the clinical practice. Some other compounds also proved to be effective in animal models and promising for clinical application as well.

Vitamin C (Ascorbic acid)
Ascorbic acid is an antioxidant and scavenger of free radicals. Animal models found it effective by systemic and local administration as well. The disadvantage of topical application is that vitamin C solution causes a rusty discoloration of the skin.6,7

Vitamin E (α-tocopherol)
Vitamin E is an effective antioxidant and biological membrane stabilizer acting by the inhibition of lipid peroxidation. Mice models found it effective orally at a dose of 400 IU/kg, although it proved to be more efficient when given subcutaneously.8

Pentoxifylline:
Orally administered pentoxifylline proved to be efficacious at a daily dose of 3×400 mg, probably acting by the decrease of vessel damage.9

Prostaglandins:
The radioprotective effect of prostaglandins is known for a long while, however it is not applicable systemically due to its toxic impacts. These harmful effects can be avoided by topical application, which has the same efficacy according to animal models.10,11

Nitroxide radical TEMPOL:
The local application of stable nitroxide radical TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) 15 minutes prior to X-ray irradiation increased new hair recovery on animal models.12
**Therapy of radiation dermatitis**

Therapy depends on the severity of skin damage. Pain killing is important at each grade: in some cases mild analgesics (Algopyrin®, Paracetamol®) are sufficient, while severe cases often require the administration of opiate analgetics (Dolargan®).

First degree radiation dermatitis heals spontaneously in 5–7 days without any medical intervention. Unpleasant symptoms like xerosis and pruritus can be alleviated by hydrophilic products (Eucerin®, Physiogel®), inflammation can be reduced by mild steroid creams (1% Hydrocortison). Alcohol and menthol containing preparations must be avoided, because they remove the natural lipids from the skin enhancing the damage.

In case of 2nd degree radiation dermatitis medical intervention is needed. Early and late erythema can be softened by external steroids. The blistering, moist dermatitis usually cures with the following conservative treatment:

1. Firstly the ruptured blisters and necrotic tissues should be removed (debridement). Beside the mechanical debridement enzyme containing products (Fibrolan®, Iruxol®) can also be used (chemical debridement). In case of intact blisters the blister’s wall should be left on the surface as a biological bonding after opening and should be removed only in case of superinfection.

2. After debridement the following products can be used for topical treatment;13,14
   - Silver and iodine containing antiseptic creams (Dermazin®, Betadine®) act by reducing the superinfection.
   - Different (e.g. paraffin) impregnated dressings (Grassolind®) are easily removable from the wounds, so further microtrauma is evitable. Additional impregnation with antiseptics (Inadine®) protects against pathogens as well.
   - Hydrocolloid dressings (Kliniderm Hydro®) can also be removed atraumatically, furthermore save against environmental contaminations, infections and irritation. Taking up the redundant matter they provide a humid environment, in which necrotic tissues are degraded by the enzymes of excretion and inflammatory cells eliminate the debris by phagocytosis. All these processes help the regeneration and significantly alleviate the pain.
   - In case of large-sized wounds biological bonding is preferable, which reduces the superficial loss of water, salt, and protein, provides mechanical defence and lighten the pain and the risk of superinfection. The origin of biological bonding can be human (allograft) or animal (xenograft). Another possibility is the keratinocyte transplantation, when in vitro raised keratinocyte layer is laid onto the wound’s surface. The drawback of this process is the relatively long time needed for breeding.

3. Finally the wound should be covered with sterile bandage.
In case of small-sized wounds, which reach the dermis surgical intervention should also be considered beside the conservative therapy, because it reduces the risk of later scarification. Tangential excision is regarded as recent technique, when thin coats of skin are removed from the wound by Humby-knife till the uninjured tissue emerges. The further therapy is conservative.

Third degree radiation dermatitis mostly requires surgical intervention. After radical excision, the transplantation of split-thickness graft (consisting of epidermis and the superficial part of dermis) is preferable. The graft can be harvested with a special, motor driven electric dermatome from the donor area, which regenerates quickly without scarification. Large-sized wounds can be covered with mesh graft, when the acquired split-thickness skin from the donor area is reticulated with a special apparatus. In this way the mesh graft is capable of covering much larger areas and the leaks heal soon in the recipient area.14

The most feared complication of skin injuries is the superinfection, which leads not only to longer healing, but in severe cases sepsis can occur resulting the main cause of death even these days. In case of superinfection microbiological culture should be taken immediately. Mild infections require only local antimicrobial therapy, while in serious cases a combination of wide-spectral antibiotics is necessary promptly, even without the result of microbiological culture.

The therapy of chronic radiation dermatitis needs tender care, because the damaged skin is vulnerable, regenerates hardly. In case of every non-healing wound malignant tumor must be excluded by histological examination. For local therapy wound dressings, especially hydrocolloid forms are suggested. Radiation fibrosis can be treated with superoxide dismutase and interferon-γ, pentoxifylline helps to improve microcirculation. Antioxidants are also recommended.2

Recent therapeutical possibilities

Helium-neon laser irradiation

Low-intensity (30 J/cm², 3 times a week) helium-neon laser has fine effect on wound healing. It stimulates cell proliferation and reactives enzymes (e.g., adenosine triphosphatase) previously inactivated due to radiation.15

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

GM-CSF stimulates wound healing by assisting the migration of monocytes into the tissues, and promoting their maturation into macrophages. Through specific receptors GM-CSF enhances keratinisation, induces angiogenesis and promotes the chemotaxis of inflammatory cells. Its most important effect is the augmentation of the proliferation
and differentiation of epidermal basal cells. Clinical trials confirmed, that gauzes impregnated with GM-CSF significantly accelerated the wound healing.\textsuperscript{16}

\textit{Transforming Growth Factor-beta 1 (TGF-\(\beta\)1)}

TGF-\(\beta\)1 has important role in wound healing: regulates the chemotaxis of macrophages and fibroblasts, and induces angiogenesis. At the same time it stimulates the synthesis of extracellular matrix proteins and decreases the activity of proteinases leading to fibrosis. Animal models pointed, that proper amount of topical TGF-\(\beta\)1 significantly improves wound healing, however at higher concentrations opposite effect is observed.\textsuperscript{17}

\textit{Orgotein}

Cu/Zn chelate with superoxide-dismutase (SOD) forms a metalloprotein called orgotein. The main component of orgotein is a scavenging enzyme that catalyzes destruction of the superoxide anion radicals. Its topical application in a concentration of 3,600 IU/mg decreases the severity of early radiation dermatitis, helps tissue healing and successfully reduces radiation induced fibrosis.\textsuperscript{18,19}

\textbf{Conclusion}

Ionizing radiation induced skin damages mostly require long-lasting, tender and costly therapy with more or less success. By the use of radioprotective agents prior to irradiation the skin defects can be prevented or decreased significantly. Currently the most commonly used agents are the topical antioxidants, but there are several investigations on animal models with other promising compounds. The therapy of the developed symptoms is also important. While the orthodox medical treatment mostly act by providing antisectic, safe environment for wound healing, new therapeutical methods, such as growth factor impregnated dressings or Helium-Neon laser interfere into the biochemical reactions on cell level improving significantly the healing process.

\textbf{References}

A. FűRÉSZ: Ionizing radiation induced skin damage


