

# Wound Care After Radiation Therapy

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**R**adiotherapy has evolved as a powerful tool for tumor control preoperatively, postoperatively, or as a sole treatment. More than 50% of cancer patients receive some form of radiation treatment and, despite improvements in radiation techniques, patients are still experiencing radiation-induced injury.

The term *radiation injury* refers to the morphologic and functional changes that can occur in noncancerous tissue as a direct result of ionizing radiation. These complications can range from mild to extremely debilitating or life-threatening.<sup>1</sup>

Ionizing radiation causes damage to tissue by means of energy transference. This energy generates highly reactive chemical products such as free ion radicals. The free radicals can subsequently combine with normal body chemicals and react with cellular components, ultimately causing intracellular and molecular damage. The primary targets of damage are cellular and nuclear membranes and deoxyribonucleic acid (DNA).

The susceptibility of an individual cell to radiation damage is directly proportional to its ability to divide. The most sensitive cells are those which divide rapidly, such as cells of the skin, bone marrow, and gastrointestinal tract.<sup>2</sup> In addition to sensitivity of the exposed cell, morbidity from radiation depends on the dose received, time over which the dose is received, volume of tissue irradiated, and quality or type of radiation.<sup>3</sup> Additional information on radiation therapy can be found in *Radiation Therapy Techniques*.

## ABSTRACT

**More than 50% of all cancer patients receive some form of radiotherapy for tumor control preoperatively, postoperatively, or as sole treatment. Radiation-induced wounds are a concern for patients and practitioners. Current research investigating alternative treatment strategies offers the hope of improved wound healing and enhanced quality of life for patients with these wounds. This paper reviews the pathophysiology of wounds following radiation treatment, the methods for treating radiation-induced wounds, and experimental treatment strategies that have been investigated.**

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## EFFECTS OF RADIATION THERAPY

### Morphologic changes

Histologically, morphologic changes can be seen in the cell after radiation exposure. With low doses of radiation, changes occur mainly in the nucleus. Under the microscope, clumping of the nuclear chromatin and swelling of the nucleus can be seen. With higher doses of radiation, the cell nucleus often becomes dense and disfigured and there may be loss of the nuclear membrane. The cytoplasm may show swelling, the mitochondria may be distorted, and the endoplasmic reticulum may degenerate.<sup>3</sup> Cellular changes resulting from low-dose radiation are probably due to an apoptotic mechanism, whereas changes related to high-dose radiation are probably due to direct cellular necrosis.

### Acute effects

Direct effects of radiation can be divided into immediate, acute (days to weeks), and delayed (months to years). Acute

effects result from necrosis of the rapidly proliferating cell lines. A transient, faint erythema may appear during the first week of treatment due to dilatation of capillaries and may be associated with an increase in vascular permeability. Radiation inhibits mitotic activity in the germinal cells of the epidermis, hair follicles, and sebaceous glands. Epilation and dryness of the skin occur.

By the third or fourth week of radiation, typical erythema is localized to the radiation field and the skin is noticeably red, edematous, warm, and tender. Larger vessels, such as arterioles, may be obstructed by fibrin thrombi, edema is

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prominent, and there may be small foci of hemorrhage. Cellular exudate is rare.

### Dry versus moist desquamation

If the total radiation dose to the skin does not exceed approximately 30 gray (Gy, the measure of radiation dose), the erythema phase is followed during the fourth or fifth week by a *dry desquamation* phase, characterized by pruritus, scaling, and an increase in melanin pigmentation in the basal layer. Within 2 months, inflammatory exudate and edema have subsided, leaving an area of brown pigmentation.

If the total radiation dose to the skin is 40 Gy or greater, the erythema phase is followed by a *moist desquamation* phase. This stage usually begins in the fourth week and is often accompanied by considerable discomfort. Bullous formation occurs suprabasally and sometimes subepidermally. Eventually, the roofs of the bullae are shed and the entire epidermis may be lost in portions of the irradiated area. Edema and fibrinous exudate persist. In the absence of infection, reepithelization of the denuded skin usually begins within 10 days. Ulcers may appear at any time from approximately 2 weeks after radiation exposure. Ulcers formed in the early stage are a result of direct necrosis of the epidermis; these ulcers usually heal but tend to recur.<sup>3,4</sup>

### Long-term effects

Approximately 1 year after radiation treatment, the epidermis is thin, dry, and semitranslucent, with vessels easily seen. Hair follicles and sebaceous glands are usually absent. Some sweat glands may also have been destroyed. In time, increasing fibrosis of the skin is present. Much of the collagen and subcutaneous adipose tissue are replaced by atypical fibroblasts and dense fibrous tissue that may cause induration of the skin and may limit movement. In radiation injury of soft tissue, fibrinous exudate accumulates under the epidermis.

Characteristic features of delayed radi-

## RADIATION THERAPY TECHNIQUES

Forms of clinical radiation include X-rays, gamma rays, and beta rays. X-rays and gamma rays are types of electromagnetic radiation; beta rays are forms of particulate radiation. The unit of radiation dose is the gray (Gy), defined as the absorbed dose of energy per kilogram of soft tissue. One Gy of radiation is equal to 1 joule of energy absorbed per 1 kilogram of tissue. The unit of radiation dose in previous use was the rad (100 rad = 1 Gy). The energy lost as radiation passes through tissue is referred to as linear energy transfer (LET); each type of radiation has its own particular LET.

Radiation used in cancer treatments can be delivered by beam sources or by brachytherapy. For external beam radiotherapy, megavoltage photon irradiation is delivered by cobalt-60 sources (gamma rays) or high-energy linear accelerators (X-rays). Brachytherapy uses radioactive sources that are placed adjacent to or within tumors, allowing high doses to be delivered to the area immediately next to the cancer source. The isotopes used most commonly in brachytherapy include cesium-137, iridium-192, iodine-125, and gold-198.<sup>1</sup>

### Low Dose vs High Dose

With low-dose radiation exposure, such as with single doses of up to 100 mGy, single-strand DNA breaks may be produced in a cell. However, this damage may be repaired at a relatively rapid rate because the remaining intact DNA strand can serve as a guide to repair. With higher doses of radiation, such as doses between 0.5 and 5 Gy, cellular death usually occurs after 1 or more reproductive divisions. Such injury is usually the result of irreparable double-strand DNA breaks. After extremely high doses of radiation (above 5 Gy), direct cell death occurs even before a reproductive division, known as *interphase death*, and is a result of direct interaction of free radicals with essential cellular enzymes and mechanisms.<sup>2</sup>

The technique of fractionation of doses is used to minimize the risk of injury to normal tissue during radiation treatments. In fractionation, the total radiation dose is delivered over a period of time, allowing for repair of sublethal injury in normal tissue and proliferation of healthy surviving cells. Likewise, a given dose of radiation administered at a low-dose rate produces less skin injury than the same total dose given at a high-dose rate. Larger doses of radiation may be tolerated, however, if they focus on small, highly specific areas of the body rather than distributed over larger areas.<sup>3</sup>

### References

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ation lesions are eccentric myointimal proliferation of the small arteries and arterioles, as well as telangiectasia (Figure 1). These changes may progress to thrombosis or complete obstruction. Delayed ulcers are more common than acute ulcers and tend to be the result of ischemia from the changes in small arteries and arterioles; they heal slowly and may persist for several years. Irradiated skin in the chronic stage is thin, hypovas-

cularized, extremely painful, and easily injured by any slight trauma or infection.<sup>3,4</sup>

## TREATMENT OF RADIATION-INDUCED WOUNDS

### Cleansers and moisturizers

Erythema may appear in the irradiated area of the skin approximately 3 weeks into

radiation treatment.<sup>5</sup> The skin should be gently cleansed with water, normal saline, or a soap solution and rinsed thoroughly to avoid excessive irritation. Friction applied to the treated area should be minimized.<sup>6</sup> Numerous skin care products are available that can be used to reduce discomfort (Table 1). For example, hydrophilic preparations (Eucerin; Beiersdorf, Norwalk, CT; Lubriderm; Pfizer, Inc, New York City, NY) that absorb water and act as mild lubricants are appropriate. Protective ointments (A+D Ointment; Schering-Plough, Kenilworth, NJ) or gels are effective for protecting dry lesions. Any products that contain alcohol or menthol should be avoided because they remove natural lipids and may worsen the skin's reaction.

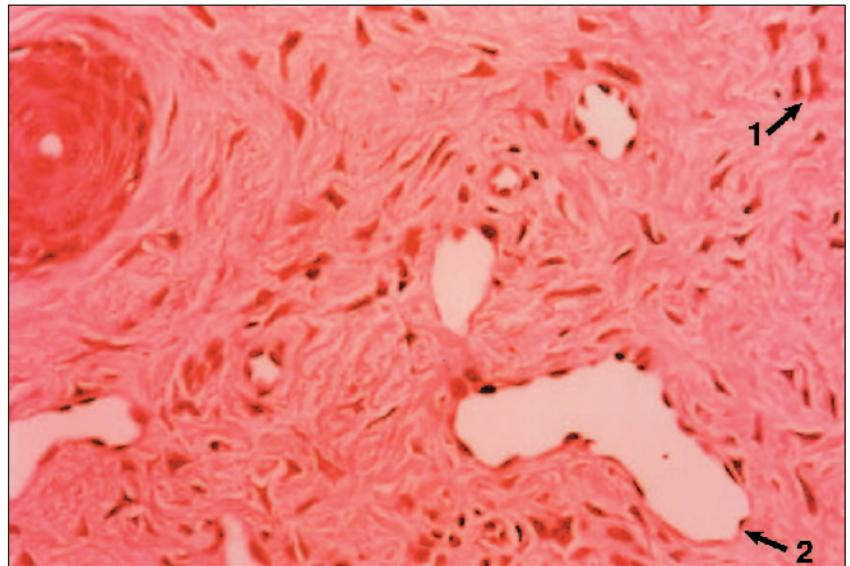
Dry desquamation may appear during this same period, with the patient's skin in the treated area appearing red or tanned, dry, itchy, and peeling. The products used to treat an erythematous reaction can also be applied in this situation. Hydrophilic preparations (Eucerin and Lubriderm, for example) protect and lubricate scaly or flaking skin resulting from the loss of sweat and sebaceous gland function.<sup>7</sup> To decrease itching, products such as colloidal oatmeal bath (Aveeno Bath; Rydelle Laboratories, Edison, NJ), cornstarch, and mild steroids such as hydrocortisone cream 1% or desoximetasone (Topicort; Medicis, Scottsdale, AZ) can be used.

Because it may have a drying effect, daily bathing is not recommended unless a low-pH, moisturizing cleanser is used. Cornstarch should not be used on moist skin or in areas that become moist, such as the axilla, breast, or groin, because it may promote fungal infection. Corticosteroids should be used with caution to reduce itching because they also delay healing by inhibiting inflammation and reducing blood flow to the skin. In addition, steroids can cause atrophy of dermal collagen, which can thin the skin and increase susceptibility to infection.

By the fourth week of treatment, moist

### Figure 1. HISTOPATHOLOGY OF CHRONIC RADIATION DERMATITIS (HEMATOXYLIN AND EOSIN)

Atypical fibroblasts (1) and telangiectasia (2) following radiation therapy. The remaining tissue is dermal fibrosis.



desquamation may occur, especially in patients with radiation treatment to the chest wall, supraclavicular region, axilla, groin, or under an intact breast. Astringent soaks, cleansers, antibiotics, and other irrigations can be used. Hydrogen peroxide has an antibacterial effect and is effective in cleansing wounds with purulent debris. However, full-strength hydrogen peroxide is harmful to granulation tissue and must be avoided.

#### Dressings

Wound dressings are beneficial because they preserve a moist environment that enhances reepithelialization, allow enzymes in the wound fluid to lyse necrotic tissue, and permit inflammatory cells to phagocytose necrotic debris and bacteria.<sup>8</sup> In addition to promoting wound healing, dressings cover the wound and protect the area from external contamination and infection; prevent soiling of clothing; and prevent further irritation, friction, or shearing. Moistened dressings or soaks with an astringent precipitate protein and cleanse, dry, and seal exudative

surfaces, preventing evaporative heat loss and decreasing inflammation and tissue desiccation (Table 1).

Dressings should be changed from 1 to 3 times daily, depending on the amount of drainage. Hydrocolloids (DuoDERM; ConvaTec, a Bristol-Myers Squibb Company, Princeton, NJ; Restore; Hollister Inc, Libertyville, IL; RepliCare; Smith & Nephew, Largo, FL) may be left in place for 5 to 7 days. Although transparent films (Tegaderm; 3M Health Care, St Paul, MN; OpSite; Smith & Nephew, Largo, FL; POLYSKIN II; Kendall, Mansfield, MA) do not adhere well to areas with skin folds, they may have advantages when compared with hydrocolloids and hydrogels. For example, the ability to irradiate through these thicker dressings without creating a possible, but unverified, bolus effect remains to be explored.

#### Antibiotics

If an infection is proved by wound culture, topical antibiotics (Neosporin; Pfizer, Inc, New York, NY; Bacitracin; Pfizer, Inc, New

**Table 1. SKIN CARE PRODUCTS USED FOR DIFFERENT RADIATION SKIN REACTIONS**

Erythema*	Dry Desquamation	Moist Desquamation	Long-term Treatments
Natural Care Gel <sup>a</sup>	All products used for erythema	Normal saline	Mild soaps (Lowila Cake <sup>b</sup> , Basis <sup>c</sup> , Dove <sup>d</sup> )
Special Care Cream <sup>a</sup>	Aloe Vesta 2-n-1 Body Wash and Shampoo <sup>e</sup>	Sterile water	Bath oils (Alpha Keri <sup>b</sup> , Lubrex <sup>f</sup> )
Radia FDG <sup>g</sup>	Aveeno Bath <sup>h</sup>	Half- or third-strength hydrogen peroxide and water	Lubricants (petrolatum, mineral and baby oils, Eucerin <sup>c</sup> )
Eucerin <sup>c</sup>	Cornstarch (not in moist skin areas)	Domeboro Soaks <sup>i</sup>	Dry skin lotions (Alpha Keri <sup>b</sup> , Lubrex <sup>f</sup> , Lubriderm <sup>j</sup> , U-Lactin <sup>f</sup> )
Lubriderm <sup>j</sup>	Mild steroids (hydrocortisone cream 1%, Topicort <sup>k</sup> )	Biolex Wound Cleanser <sup>a</sup>	Creams (Alpha Keri <sup>b</sup> , Nivea <sup>c</sup> )
A+D Ointment <sup>l</sup>		CarraKlenz Wound Cleanser <sup>g</sup>	Thick preparations (Eucerin <sup>c</sup> , Aquaphor <sup>c</sup> )
Aloe Vesta 2-n-1 Protective Ointment <sup>e</sup>		Film dressings: Tegaderm <sup>m</sup> , OpSite <sup>n</sup> , POLYSKIN II <sup>o</sup>	
		Hydrocolloid dressings: DuoDERM <sup>e</sup> , Restore <sup>p</sup> , RepliCare <sup>b</sup>	
		Gel dressing: Vigilon <sup>q</sup>	
*Avoid products that contain alcohol or menthol			
<sup>a</sup> Bard, Murray Hill, NJ	<sup>f</sup> Allerderm Laboratories, Petaluma, CA	<sup>l</sup> Schering-Plough, Kenilworth, NJ	
<sup>b</sup> Westwood-Squibb, Buffalo, NY	<sup>g</sup> Carrington, Irving, TX	<sup>m</sup> 3M Health Care, St Paul, MN	
<sup>c</sup> Beiersdorf, Norwalk, CT	<sup>h</sup> Rydelle Laboratories, Edison, NJ	<sup>n</sup> Smith & Nephew, Largo, FL	
<sup>d</sup> Unilever, London, UK, and Rotterdam, The Netherlands	<sup>i</sup> Bayer Consumer Care Division, Morristown, NJ	<sup>o</sup> Kendall, Mansfield, MA	
<sup>e</sup> ConvaTec, a Bristol-Myers Squibb Company, Princeton, NJ	<sup>j</sup> Pfizer, Inc., New York City, NY	<sup>p</sup> Hollister Inc, Libertyville, IL	
	<sup>k</sup> Medicis, Scottsdale, AZ	<sup>q</sup> Bard Medical Division, Covington, GA	

York, NY) should be used. A systemic antibiotic may be needed if the area does not heal. Some clinicians recommend use of silver sulfadiazine 1% cream (generic version; Watson Pharmaceuticals, Corona, CA; Thermazene; Kendall, Mansfield, MA) as an effective preparation against Gram-positive and Gram-negative organisms and against *Candida albicans*.

### Treatment for xerosis

Over the long term, irradiated skin often develops chronic, localized xerosis. For this condition, mild soaps and bath oils may be used during bathing. Neutral soap preparations are made with synthetic detergents and have a pH of less than 7.5 (Lowila Cake; Westwood-Squibb, Buffalo, NY; Dove; Unilever, London, UK, and Rotterdam, The Netherlands). Basis (Beiersdorf, Norwalk, CT) contains a higher amount of fat that leaves a film of protective oil on the skin. Some skin cleansers (Aloe Vesta 2-n-1 Body

Wash and Shampoo; ConvaTec, a Bristol-Myers Squibb Company, Princeton, NJ) are formulated to cleanse and moisturize the skin while preserving its naturally low pH. Lubricants such as petrolatum and mineral and baby oils are generally more effective, but tend to be less aesthetically pleasing to patients.

Dry skin lotions, creams, or thicker preparations may be used to lubricate the skin, prevent fissures, and keep the skin pliable. Lotions are suspensions of powder in water that provide a protective drying and cooling effect while leaving a film of powder on the skin. Creams are emulsions of oil in water that are water washable and completely absorbed into the skin.

### Protection

In some patients, irradiated skin may appear normal after completion of radiation therapy. However, changes may eventually become evident and adversely affect a

patient's quality of life. The higher the dose of radiation received, the more likely that changes, such as fibrosis of tissues and small blood vessels, will be delayed. Patients should be taught to protect irradiated skin from excessive sun exposure and other trauma because the skin's ability to respond to trauma is reduced and the skin heals more slowly if injured. The patient should use a sunscreen with an SPF of 15 or higher if he or she expects to be in direct sunlight for more than 15 minutes.

In rare cases, radiation wounds may be so severe that skin grafting may be necessary. Under these circumstances, certain dressings (Table 2) used for thermal burns may be applied to the radiation wounds and donor graft sites.<sup>9-21</sup>

## EXPERIMENTAL TREATMENT STRATEGIES

Investigation into possible treatments for radiation-induced skin injury has includ-

ed growth factors, cytokines, antioxidants, topical steroids and nonsteroidal anti-inflammatory preparations, aloe vera, and lasers.

### TGF-beta 1

Transforming growth factor beta-1 (TGF-beta 1) is one of several proteins that have important roles in wound healing. After tissue injury, TGF-beta 1 and platelet-derived growth factor are released from platelets and help modulate chemotaxis of macrophages and fibroblasts into the wound. TGF-beta 1 stimulates the formation of extracellular matrix proteins, collagen, and fibronectin by increasing these protein messenger ribonucleic acid (RNA) levels in the wounded tissue. In addition, TGF-beta 1 increases angiogenesis, probably by modulating macrophages to release factors that lead to neovascularization.

In a study using a rat model, Nall and colleagues evaluated the effect of TGF-beta 1 on wound healing and random flap survival in a setting of chronic irradiation.<sup>22</sup> The results of the study demonstrated that TGF-beta 1 improved tensile strength in the irradiated and nonirradiated groups. TGF-beta 1 also improved flap survival in all groups, but significantly in the irradiation plus TGF-beta 1 group. Because the most mature collagen at the wound edge was present in the TGF-beta 1 group, the researchers concluded that TGF-beta 1 improves wound healing and random flap survival in irradiated and nonirradiated rat skin.

Bernstein and colleagues<sup>23</sup> studied the effect of TGF-beta 1 on healing of radiation-impaired wounds using a guinea pig model. Statistically significant increases in wound bursting strength were seen in irradiated wounds treated with 1 gram and 5 grams of TGF-beta 1 when compared with control wounds. Wounds treated with 1 gram of TGF-beta 1 increased 87% in strength versus paired-matched controls. Wounds that received

**Table 2. DRESSINGS USED FOR SEVERE RADIATION WOUNDS THAT MAY REQUIRE SKIN GRAFTING**

Type of Dressing	Applications
Biosynthetic and Synthetic (Biobrane*, OpSite†, and Tegaderm‡)	Biobrane: Protects clean, superficial, partial-thickness burns; can be used to protect a wound between widely meshed autograft; also used for intermediate closure of an excised wound until autograft becomes available; covers donor graft sites OpSite or Tegaderm: Covers clean partial-thickness wounds and donor sites; reduces pain from wounds; and provides moist environment for reepithelialization
Artificial Skin (Integra§)	Dermal substitute used for closure of excised full-thickness burns
Bioengineered Skin (Apligraf¶)	Indicated for chronic venous and diabetic foot ulcers; can serve many functions of human skin, including providing a barrier for the wound against mechanical damage and infection, producing structural and regulatory substances (eg, growth factors or cytokines), and interacting with underlying tissue to promote more effective wound care; low antigenicity, greater likelihood of graft acceptance, and greater proliferative potential

\*Bertek, Morgantown, WV  
†Smith & Nephew, Largo, FL  
‡3M Health Care, St Paul, MN

§Integra Life Sciences, Plainsboro, NJ  
¶Organogenesis, Canton, MA, and Novartis Pharmaceuticals Corporation, East Hanover, NJ

5 grams of TGF-beta 1 increased 92% versus matched controls. Wounds treated with 20 grams of TGF-beta 1, however, were noted to be 28% weaker than paired controls. The researchers commented that total doses of TGF-beta 1 must be closely monitored in clinical applications to avoid effects opposite to those desired.

### TGF-beta 1 inhibitors

TGF-beta 1 inhibitors have been demonstrated to decrease the amount of late-radiation fibrosis. TGF-beta 1 is a cytokine considered to act as a master switch for tissue fibrosis—a major form of late radiation damage. The 3 main biologic activities of TGF-beta 1 are regulation and general inhibition of cell growth, immunosuppression, and regulation of the deposition of extracellular matrix components. The role of TGF-beta 1 in wound healing is related

primarily to its ability to control the homeostasis of the extracellular matrix. TGF-beta 1 causes remodeling of extracellular matrix by stimulating cells to increase the synthesis of most matrix proteins, decrease production of matrix-degrading proteases, increase production of inhibitors of these proteases, and modulate the expression of integrins. With elevated production of TGF-beta 1, tissue fibrosis can occur. The predominant characteristics of radiation fibrosis are massive deposition of extracellular matrix and excessive fibroblast proliferation. In addition, some loss of feedback inhibition is present in fibrosis and, consequently, chronic, long-term myofibroblast activation is sustained.

Studies involving either in vitro research of human fibroblasts and keratinocytes or mice models have demonstrated that TGF-beta 1 induction is a general response of cells to ionizing radiation, and TGF-beta 1

overexpression exists throughout all phases of fibrosis development.<sup>24,25</sup> Fibrosis and scar development are favored by TGF- $\beta$  1's bimodal action on cell proliferation, with inhibition of epithelial cells and activation of fibroblasts. In addition, TGF- $\beta$  1's ability to induce apoptosis in certain cell types can favor parenchymal damage and replacement by fibrotic tissue. New experimental data obtained from animal studies and human fibroblast research have shown use of liposomal Cu/Zn superoxide dismutase (SOD) is effective in reducing long-standing radiation fibrosis.<sup>26</sup> A possible mechanism through which this may occur is by a SOD-induced down-regulation of TGF- $\beta$  1 secretion by myofibroblasts.<sup>26</sup>

### Orgotein

A growing body of evidence supports a causative role of oxidative stress in fibrogenesis. Therefore, much research has been conducted on the use of other antioxidant factors to ameliorate radiation-induced adverse effects. For example, the drug orgotein has been studied for its possible protective effect on radiation cystitis and proctitis. Orgotein is a metalloprotein in the form of a Cu/Zn chelate with SOD. SOD, the main component of the drug, is a scavenging enzyme that catalyzes destruction of the superoxide anion radicals formed by irradiation. A randomized trial by Nielsen and colleagues,<sup>27</sup> however, showed no effect of orgotein on the radiation response or on any radiation-induced adverse effects. In addition, orgotein treatment was discontinued in 5 of 19 patients in that trial due to development of a local reaction at the orgotein injection site in the form of subcutaneous/cutaneous infiltration and redness.

A more recent study conducted by Sanchiz and colleagues<sup>28</sup> evaluated the use of orgotein administered with radiotherapy in patients with bladder cancer. They concluded that orgotein is effective in decreasing acute radiation-induced damage and in preventing the appear-

ance of more delayed disorders. Another study from Cividalli and colleagues<sup>29</sup> investigated the radioprotective effects of orgotein on normal skin and malignant murine tissue *in vivo*. No effects of orgotein were seen on tumor radiation response; however, a protective effect was observed on normal skin for early and permanent damage. More rapid tissue healing was noted in the instance of early damage.

### Topical vitamin C solution

Dermatitis is often a problem for patients during radiation treatment and studies have assessed the use of topical vitamin C solution for prevention of radiation dermatitis, in keeping with the concept of the use of antioxidants.<sup>30,31</sup> Ascorbic acid is an antioxidant and scavenger of peroxyl radicals. Ascorbic acid solution has the potential to protect nonmalignant tissue from radiation and improve collagen synthesis, although some patients have reported a rusty discoloration of their skin from the vitamin C solution.<sup>30,31</sup> Okunieff<sup>30</sup> demonstrated that ascorbic acid administered systemically to mice 50 minutes before whole-body radiation significantly increased the dose of radiation required to obtain skin desquamation. He proposed that after high-dose ascorbic acid, the radiation dose given to cancer patients could be increased without increasing acute complications. Okunieff did not determine, however, whether late-reacting tissues are similarly protected by ascorbic acid. A study conducted by Halperin and colleagues<sup>31</sup> attempted to determine the value of topical ascorbic acid in preventing radiation dermatitis in patients with primary or metastatic brain tumors requiring external beam irradiation. They were unable to demonstrate a significant radioprotective effect from the ascorbic acid solution, which may not be surprising given that little ascorbic acid is absorbed topically.

### Topical corticosteroids, glucocorticoids, and NSAIDs

Topical corticosteroids have been shown to have an anti-inflammatory effect in radiation dermatitis and, therefore, are commonly prescribed to treat this condition.<sup>32,33</sup> It has been determined that acute and chronic effects of radiation are accompanied by excessive production of eicosanoids (prostaglandins, prostacyclin, thromboxanes, and leukotrienes).<sup>34</sup> These endogenous mediators may be responsible for much of the vasodilatation, increased vascular permeability, thrombosis, and chemotaxis observed after radiation exposure. Glucocorticoids are known to inhibit eicosanoid synthesis by interfering with phospholipase A<sub>2</sub>, and nonsteroidal anti-inflammatory drugs (NSAIDs) prevent prostaglandin/thromboxane synthesis by inhibiting cyclooxygenase.<sup>34</sup> Several studies have shown that administration of drugs belonging to either the glucocorticoid or NSAID groups attenuate, to a large extent, the effects of radiation in humans.<sup>32-34</sup>

In a study by Glees and colleagues,<sup>33</sup> 2 different steroid creams—1% hydrocortisone and 0.05% clobetasone butyrate—were compared in patients undergoing radiation therapy for breast cancer. The majority of patients using either cream derived benefit from their soothing effects, but a significant difference in intensity of reactions was noted. Patients using hydrocortisone developed much less severe radiation reactions, even though they received similar radiation doses as the other group of patients.<sup>33</sup> The authors concluded that of the 2 creams, 1% hydrocortisone is superior to clobetasone butyrate but, in their opinion, neither cream was efficacious enough to be recommended as a first choice for initial treatment.

A more recent study by Simonen and colleagues<sup>34</sup> examined the effects on erythema of 1% topical indomethacin and 1% topical hydrocortisone applied before

and during radiotherapy.<sup>34</sup> Differing intensities of reactions in the 2 treatment arms did not occur until the third week after starting treatment. At that time, patients treated with indomethacin spray developed more severe erythematous reactions until about 5 weeks after starting therapy. The researchers proposed that hydrocortisone applied at the time of radiation produces a lasting agitation of the inflammatory cell infiltrate and, as a result, beneficial effects of hydrocortisone can still be seen several weeks after application is discontinued.

### Aloe vera gel

Studies have evaluated aloe vera gel as a prophylactic agent for radiation-induced skin toxicity.<sup>35,36</sup> Several pharmacologically active compounds that have been discovered in the aloe vera plant may help to decrease inflammation. One of these substances is a carboxypeptidase, which can hydrolyze bradykinin and angiotensin I. Salicylic acid is also present and can be converted into a salicylate that will inhibit prostaglandin synthesis. The magnesium lactate in aloe vera can inhibit histidine decarboxylase and act as an antihistamine. Aloe vera has also been demonstrated to possess antibacterial and antifungal properties.

To investigate whether an aloe vera gel might help prevent radiation-induced dermatitis, Williams and colleagues<sup>36</sup> conducted 2 Phase III randomized trials that compared aloe vera gel with placebo or no treatment. Neither trial showed any significant benefit from use of aloe vera. In the 2 trials, the distribution of maximum dermatitis severity scores was nearly identical in both treatment arms, regardless of whether they were scored by the patients or by the health care providers.

A recent prospective randomized trial by Olsen and colleagues<sup>37</sup> attempted to determine whether the use of mild soap and aloe vera gel versus mild soap alone would decrease the incidence of skin

reactions in patients undergoing radiation therapy. Results of the trial showed that if the cumulative radiation dose was low (2700 cGy) and aloe was added to the regimen, the difference in the radiation effect was not significant. The median time to skin change was 2 weeks in both treatment arms. When the cumulative dose was greater than 2700 cGy, however, the median time was 5 weeks before any skin changes in the aloe and soap arm versus 3 weeks in the soap only arm. The researchers concluded that when the cumulative radiation dose increases over time, adding aloe to the soap regimen seems to have a protective effect.

### Helium-neon laser irradiation

Low-intensity helium-neon laser irradiation was demonstrated by Schindl and colleagues<sup>38</sup> to have a beneficial effect on impaired wound healing of recalcitrant skin ulcers after radiation therapy. Laser irradiation can enhance metabolic pathways by several different mechanisms, including activation of previously partially inactivated enzymes such as adenosine triphosphatase (ATPase), induction of reactive oxygen species, stimulation of calcium influx and mitosis rate, and augmented formation of messenger ribonucleic acid (mRNA) and protein secretion. Laser treatment also enhances cell proliferation and motility of fibroblasts and keratinocytes. Evidence exists for the possible improvement of skin circulation and induction of angiogenesis. In the study by Schindl and colleagues,<sup>38</sup> patients with recalcitrant radiation ulcers of the skin after mastectomy were treated with a 30-mW helium-neon laser at an energy density of 30 J/cm<sup>2</sup>, 3 times weekly until successful closure of the ulcers.

### GM-CSF

The effectiveness of granulocyte-macrophage colony-stimulating factor (GM-CSF) in managing acute radiation dermatitis, based on its therapeutic effect in burn

patients, has been investigated. Application of GM-CSF is believed to stimulate wound healing by various processes, including promoting migration of monocytes into tissues, stimulating maturation of monocytes into macrophages, increasing fibroplasia and keratinization through specific receptors, inducing growth of new blood vessels, and promoting chemotaxis of inflammatory cells that are involved in the process of healing.<sup>39</sup> The most important role of GM-CSF is its stimulation of proliferation and differentiation of basal epithelial stem cells. The systems of dendritic cells, keratinocytes, fibroblasts, and synovial cells of the dermis and of the submucosa are also regulated.

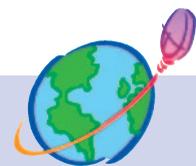
Kouvaris and colleagues<sup>39</sup> investigated the effectiveness of GM-CSF impregnated gauze in preventing or healing radiation-induced dermatitis. The use of GM-CSF impregnated gauze along with steroid cream versus steroid cream alone was studied in 61 patients receiving radiation treatments for vulvar carcinoma. The use of the GM-CSF impregnated gauze showed statistically significant reduction in the duration of symptoms, the healing period of dermatitis, and the pain and severity of dermatitis. There were no cutaneous or systemic toxicities or allergic reactions detected with cutaneous GM-CSF application.

## CONCLUSIONS

Radiation-induced wounds are an increasing concern for patients and practitioners. Clinicians should familiarize themselves with the clinical presentation of the burn wounds and histologic changes that occur after radiation treatment. A thorough knowledge of the treatments for these wounds is equally important. Alternative treatment strategies currently being investigated offer the hope of improved wound healing and enhanced quality of life for patients following radiation treatment for cancer. ●

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