Photo courtesy of
©liujunrong/123RF

Sponsored by Quest Healthcare,
a Division of Quest Products, LLC

CURRENT PREVENTION AND MANAGEMENT OF RADIATION DERMATITIS: A FOCUS ON PHARMACOLOGIC AND EMERGING TREATMENTS

Rita Sagurton Herman APN-BC

Ms. Rita Sagurton-Herman FNP-BC, is currently a Primary Care Specialist in Red Bank New Jersey. She has over 23 years of diverse experience as a RN and over 22 years as a FNP.

Ms. Herman received her BSN in 1977 from Fairleigh Dickinson University and her MSN in 2000 from Monmouth University. She is Board Certified by the American Nurses Credentialing Center and has experience in many fields including Intensive Care, Oncology, Primary Care, Geriatrics, Allergy and Asthma, Diabetes, Pain Management and Mental Health.

She is currently working at Health Care for Life in Eatontown, N.J.

Radiation therapy is a common treatment for various types of cancer, including breast, head and neck, and skin cancers.[1] An estimated 50% of patients with cancer in North America will be treated with radiation therapy during their illness. Unfortunately, the same mechanism that is effective in treating cancer also causes major adverse consequences.[2] The energy delivered to the irradiated body part can produce local inflammation and reactive oxygen species that damage cellular structures, including cell membranes and DNA.

Although effective, the use of radiation therapy is often limited by these adverse dermatologic changes.[1] These include acute effects such as erythema and desquamation, and late effects such as fibrosis. Unfortunately, radiation dermatitis is extremely common, affecting up to 95% of patients who receive radiation therapy.[1,2] Radiation dermatitis can have major adverse consequences on patients' quality of life. Although routine nonpharmacologic skin care measures are accepted as standard care, unfortunately, evidence is limited for pharmacologic therapies. Therefore, this review provides a summary of the pathophysiology, presentation, and management of radiation dermatitis, with a focus on pharmacologic and emerging treatments.

EPIDEMIOLOGY

Radiation therapy is commonly employed in treatment of anal, breast, head and neck, sarcoma, skin, and vulvar cancers.[2] Because the irradiated area is close to the skin, radiation dermatitis is common in patients with these cancers. Various patient- and treatment-related factors increase the risk of radiation dermatitis. For example, risk increases with irradiation of more sensitive areas, such as the abdomen, anterior of the neck, chest, extremities, and face. Patients with breast reconstructions and implants are at increased risk of severe radiation dermatitis because these procedures can reduce the skin's ability to dissipate heat.[3] Additionally, older age increases risk because of aging cell lines and loss of collagen.[4] Likewise, patients who smoke experience disruptions in healing due to impaired oxygenation. Other risk factors include obesity, poor nutritional status, chronic sun exposure, and disorders of connective tissue (eg, systemic lupus erythematosus) and skin (eg, acne, psoriasis).

Treatment-related factors that increase risk of radiation dermatitis include higher total radiation dose and use of bolus radiation therapy.[4] Concurrent medical therapy also plays a role; use of epidermal growth factor inhibitors has been associated with an approximate 2-fold increase in radiation dermatitis because of their effect on increasing radiosensitivity.[5]

PATHOPHYSIOLOGY

Ionizing radiation contributes to the pathophysiology of radiation dermatitis by generating free radicals and reactive oxygen species.[1,2,6] These cause damage to DNA and adverse changes to components of the skin; thus the same mechanism used to kill cancer cells is also responsible for radiation dermatitis. Acute dermatitis often presents shortly after irradiation, but because these effects are cumulative throughout treatment, changes may not occur for weeks after treatment initiation. Acute changes are reflective of both direct tissue injury and local inflammation. For example, erythema is likely associated with

www.questhealthcare.net
www.alocane.com

capillary dilation and vascular permeability due to production of inflammatory mediators. Skin dryness can result from destruction of sebaceous glands and hair follicles. Over time, chronic changes may involve modifications to the dermal and subcutaneous vascular and connective tissue, potentially resulting in telangiectasia and hyper- or hypopigmentation.

PRESENTATION AND DIAGNOSIS

Presentation of radiation dermatitis differs based on acute versus chronic skin changes.[1,2] Changes that occur within 90 days of radiation therapy are categorized as acute reactions. These typically occur within days to weeks of therapy, and often involve early erythema that often abates within days. Other acute changes may include dryness, loss of hair, and hyperpigmentation. In later weeks, dry desquamation can occur, causing itchiness, flaking, and scaling of the skin. Higher radiation doses may cause more severe cases, in which moist desquamation occurs and causes edema, exudate, and bullae formation.

Chronic radiation dermatitis occurs 90 or more days after completion of radiation therapy, but may develop over a course of years.[1,2] Signs include dermal atrophy, fibrosis, vascular injury, thinning of the epidermis, and thickening of the dermis. Severe cases may result in dermal necrosis, and as a result, infection.

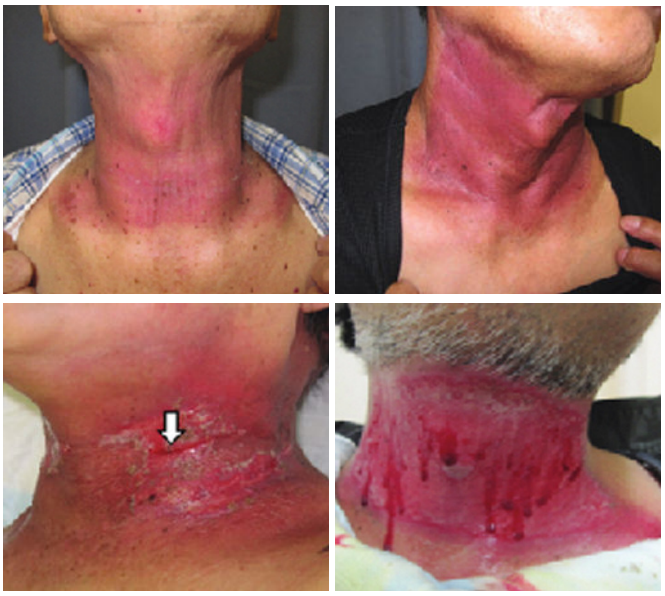
Grading of the severity of radiation dermatitis is important to assessment and management; however, no consensus approach exists.[2] The most commonly used assessment scales include the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) scale.[2,7] Both systems implement scores representing similar severity and presentation (Table 1). Illustrations of the grades of radiation dermatitis based on CTCAE criteria are presented in Figure [1,8]

Table 1. Common scoring systems for severity of radiation dermatitis.[2,7]

Score	Scoring System and Definitions	
	NCI CTCAE	RTOG/EORTC
0	No change	
1	Erythema, dry desquamation	
2	Moderate to brisk erythema Patchy, moist desquamation Only skin folds and creases affected Moderate edema	Bright erythema Moist desquamation Edema
3	Moist desquamation in areas other than skin folds and creases Bleeding induced by minor trauma or abrasion	Confluent moist desquamation Pitting edema
4	Life-threatening consequences Skin necrosis or ulceration of full thickness dermis Spontaneous bleeding Skin graft indicated	Ulceration Hemorrhage Necrosis
5	Death	

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organization for Research and Treatment of Cancer; NCI, National Cancer Institute; RTOG, Radiation Therapy Oncology Group.

Figure 1. Grade 1 through 4 radiation dermatitis based on CTCAE criteria.[8,a]



[a]Panels represent dermatitis of Grade 1 (top left), 2 (top right), 3 (bottom left), and 4 (bottom right).

The diagnosis of radiation dermatitis is a clinical one, relying on assessment of skin changes and recent exposure to radiation therapy, as well as consideration of predisposing risk factors.[2,9] The reaction should be differentiated from other similarly presenting cutaneous conditions, including contact dermatitis, herpes zoster, radiation port dermatophytosis, and rarely Stevens-Johnson syndrome or toxic epidermal necrolysis.

GUIDELINE RECOMMENDATIONS ON PREVENTION AND MANAGEMENT

Prevention and management of radiation dermatitis can be challenging.[1,2] The mechanisms and properties of numerous prescription and non-prescription agents seem promising in managing radiation-induced skin changes. However, to date, studies have reported conflicting or negative results for many of these agents.[10-12] Thus, current practice is often variable and rooted in clinical experience.[2] In 2013, the Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group performed a systematic literature review and produced a guideline for the prevention and treatment of acute and late radiation reactions.[13] Because it is one of the most widely recognized treatment guidelines for management of radiation dermatitis, recommendations from the MASCC panel are summarized below.

Nonpharmacologic measures

General measures to prevent radiation dermatitis include nonpharmacologic modalities such as wearing loose-fitting clothing at the site of irradiation, avoiding tobacco and alcohol, and maintaining adequate hydration.[1,2] Patients undergoing radiation therapy were historically instructed to not wash the irradiated area; however, recent findings have challenged this practice.[13] Several randomized controlled trials (RCTs) demonstrated that washing irradiated skin with water and mild soap demonstrated reduced itching, erythema, and desquamation compared with water alone.[1,13] Therefore, the MASCC guideline strongly recommends gentle washing with or without a mild soap or shampoo.[13]

Pharmacologic measures

Various pharmacologic interventions have been evaluated because they have a mechanism suggestive of benefit; however, few have evidence sufficient to justify recommendations in favor of their use.[13] These interventions and recommendations on their use are summarized below and in Table 2.

Table 2. Summary of MASCC recommendations for pharmacologic measures in radiation dermatitis.[13]

Intervention	Proposed Mechanism	MASCC Recommendation[a,b]
Topical		
Corticosteroids	Anti-inflammatory properties; inhibition of cytokine production	Strong recommendation for preventive use, particularly mometasone (Level II, Grade B)
Silver sulfadiazine	Anti-inflammatory, antibacterial, barrier-enhancing properties	Weak recommendation for preventive use (Level II, Grade B)
Aloe vera	Anti-inflammatory properties	Strong recommendation against preventive use (Level I, Grade A)
Trolamine	Anti-inflammatory, antibacterial, barrier-enhancing properties	Strong recommendation against preventive use (Level I, Grade A for prevention; Level II, Grade C for treatment)
Sucralfate	Anti-inflammatory, antibacterial, barrier-enhancing properties	Insufficient evidence for preventive use or treatment (Level II, Grade C)
Ascorbic acid	Antioxidant; free radical scavenging properties	Insufficient evidence for preventive use (Level II, Grade C)
Dexpanthenol	Barrier-enhancing properties	
Hyaluronic acid	Stimulation of fibrin development, granulocyte and macrophage mobility, and fibroblast proliferation	
Petroleum-based ointments	Barrier-enhancing properties	
Systemic		
Pentoxifylline + vitamin E	Microcirculatory enhancement; improved tissue compliance	Insufficient evidence for preventive use (Level II, Grade B for treatment)
Proteolytic enzymes	Analgesic, anti-inflammatory properties	Insufficient evidence for treatment (Level II, Grade B for treatment)
Pentoxifylline	Microcirculatory enhancement	Insufficient evidence for treatment (Level II, Grade C)
Sucralfate	Mucoprotective properties	
Zinc		

Abbreviation: MASCC, Multinational Association for Supportive Care in Cancer.

[a]Levels of evidence: I, meta-analyses and randomized trials with high power; II, randomized trials with low power; III, nonrandomized trials; IV, descriptive and case studies; V, case reports and clinical examples.

[b]Grade of recommendation: A, Level I evidence or multiple consistent findings of Level II through IV evidence; B, generally consistent Level II through IV evidence; C, inconsistent or low-power evidence; D, little or no evidence.

Prevention

Among various interventions, topical corticosteroids and silver sulfadiazine cream appear to more consistently demonstrate efficacy than other measures.[13] Topical corticosteroids have antiinflammatory effects that inhibit the increase in cytokine production caused by irradiation.[10-12] Several trials in patients with breast cancer undergoing radiation therapy have compared topical corticosteroids with control groups of either no treatment, an emollient, dexpanthenol, or placebo.[13] The studies evaluated beclomethasone spray, mometasone furoate combined with an emollient, and methyl-prednisolone. Treatment with topical corticosteroids demonstrated a trend in reducing maximum toxicity grade and intensity of skin erythema. Evidence appeared to be strongest for mometasone furoate, which in one double-blind RCT, demonstrated significant reductions in the mean grade of itching and discomfort or burning. Despite the small sample sizes of these studies, the MASCC panel strongly recommends use of prophylactic topical cortico-steroids (eg, mometasone) to reduce discomfort or burning and itching.

Aloe vera is a commonly used natural topical agent with anti-inflammatory properties.[10,13] It contains vitamins, enzymes, minerals, and amino acids that contribute to healing. However, several RCTs found no benefit with aloe vera compared with cream, mild soap, or no treatment.[13] While studies have not generally demonstrated safety concerns with aloe vera, the MASCC panel strongly recommends against its use. Nonetheless, a recent survey of radiation oncologists reported that approximately half of respondents used aloe in prevention and treatment of radiation dermatitis.[14]

Silver sulfadiazine also has anti-inflammatory, anti-bacterial, and barrier-enhancing properties.[10-12] Silver sulfadiazine cream has been investigated in a single trial of women undergoing radiation therapy for breast cancer.[13] Compared with standard skin care, silver sulfadiazine cream was associated with improved total skin injury scores after 6 weeks. The MASCC panel makes a weak recommendation for the prophylactic use of silver sulfadiazine cream in breast cancer.

Trolamine, a topical non-steroidal anti-inflammatory agent, is believed to recruit macrophages and stimulate granulation tissue.[13] However, several RCTs demonstrated no benefit in comparisons of trolamine with control groups of no treatment or topical emollients, and the MASCC panel strongly recommends against the use of trolamine for prevention or treatment of radiation dermatitis.

Various other agents were reviewed by the MASCC panel, but were deemed to have insufficient supporting evidence to warrant recommendations.[13] These include sucralfate, hyaluronic acid, ascorbic acid, petroleum-based ointments, and dexpanthenol (an analog of vitamin B5). The mechanisms of action and MASCC statements on these agents are summarized in Table 2.

Treatment

Recommendations for treatment of radiation dermatitis are limited.[13] General skin care measures that promote moist healing and improved cell growth, division, and migration (include hydrogel and hydrocolloid dressing) are often used;

however, the MASCC panel concluded evidence for these dressings is currently insufficient.[15] Similar statements were issued regarding sucralfate and trolamine. For late radiation dermatitis, the panel makes a weak recommendation for use of long-pulsed dye laser in treatment of telangiectasia. For cutaneous fibrosis, two uncontrolled studies of pentoxifylline alone or combined with vitamin E were available; however, these were insufficient to support recommendations.

EMERGING TREATMENTS

Photobiomodulation

In recent years, photobiomodulation using low-level light therapy has gained greater attention as an option in prevention and management of radiation dermatitis.[16] This therapy involves application of low-intensity light in the visible and near-infrared spectrum before and/or after radiotherapy sessions.[17] While not fully understood, the mechanism of photobiomodulation is believed to be related to photon absorption, which causes release of nitric oxide and increases in growth factor production, cellular proliferation, and extracellular matrix deposition.[16] Several clinical trials have evaluated photobiomod-ulation, predominantly in patients with breast cancer, and have demonstrated reductions in the incidence and severity of radiation dermatitis and improvements in pain and quality of life.[16-18] There is currently no consensus on the role of photobiomodulation in radiation dermatitis, and evidence for this therapy will continue to evolve.[16]

Topical analgesics, antiseptics, and antioxidants

Alocane Plus is a topical ointment containing 4% lidocaine (a topical analgesic) and 0.13% benzalkonium chloride (a topical antiseptic), along with other ingredients such as aloe vera and tocopherol acetate (vitamin E).[19] Lidocaine is a local anesthetic that exerts its analgesic effects through inhibition of voltage-gated sodium channels in neurons, thus preventing the generation and conduction of nerve impulses.[20] Lidocaine has long been used to numb regions of skin and relieve pain due to skin wounds.[21] The local anesthetic effect of lidocaine is rapid, and the duration of effect ranges from 3 to 8 hours based on the dose, route, and area of administration. Benzalkonium chloride, one of the most common active ingredients in disinfectants, is an antiseptic with activity against bacteria, fungi, and viruses.[22] As a cationic surfactant, benzalkonium chloride causes lysis of bacterial cell walls, and has demonstrated reductions in bacterial biofilm burden in *in vitro* studies and murine models.[23,24]

CURRENT MANAGEMENT AND CONSIDERATIONS

Given the limited number of interventions with supporting evidence, some experts have developed local treatment guidelines that describe their approach to prevention and management of radiation dermatitis.[9,15,25] Prior to irradiation, topical moisturizers, gels, and dressings should be avoided because they may produce a bolus effect, increasing the dose of radiation delivered to the epidermis. Generally, topical corticosteroids are utilized to reduce erythema and pruritis. Low- to medium-potency agents (eg, mometasone furoate 0.1%, hydrocortisone 1%) applied once or twice daily are preferred, and therapy can be escalated to higher-potency corticosteroids if symptom relief is inadequate. The duration of topical corticosteroid use is recommended to be limited to a 3- to 5-day period because long-term use may cause skin atrophy and reduce blood flow to the skin.

Routine skin care, including hydration, hygiene, and protection should be encouraged in all patients to manage erythema, pruritis, and desquamation.[9,15,25] Patients who develop grade 1 radiation dermatitis generally only require these general skin care measures. Dry desquamation may be managed with hydrophilic moisturizers or medium-potency topical corticosteroids (eg, fluticasone propionate 0.05% cream, hydrocortisone valerate 0.2% ointment), which can mitigate pruritis and irritation; oral antihistamines may also be considered. Patients with grade 2 to 3 dermatitis and moist desquamation typically receive dressings over the areas of skin sloughing, and may benefit from topical and/or systemic antibiotics to prevent infection. Adjunctive topical or oral analgesic therapy may also promote comfort in patients with moist desquamation. Patients with grade 4 radiation dermatitis should be managed on a case-by-case basis, and may require multidisciplinary management including a wound specialist, dermatologist, and radiation oncologist. These patients may require surgical debridement or skin graft, as well as systemic or topical antibacterials to prevent or treat infection.

Testimonials from clinicians also support use of emerging therapies in radiation dermatitis, including Alocane Plus. A clinician described use of Alocane Plus for relief of pain and itching associated with radiotherapy, particularly in patients with breast cancer and postradiotherapy soreness and itching. A typical protocol used by this clinician includes application of Alocane Plus 3 to 4 times daily between the twelfth and twentieth days of radiotherapy. Patients may continue using Alocane Plus for up to 2 weeks after completion of treatment. Adjunctive treatments may also include moisturizing cream or corticosteroid cream, which are applied after Alocane Plus. Patients treated with this protocol reported mild pain relief and decreased pruritis, and typically experienced resolution of radiation dermatitis within a month.

CONCLUSION

Radiation dermatitis is an adverse effect that occurs in nearly all patients with cancer who receive radiation therapy. Symptoms including erythema, pruritis, and desquamation, can have serious impacts on quality of life. Despite the incidence of radiation dermatitis, few interventions have strong evidence supporting use in prevention or treatment. Currently, only topical corticosteroids and silver sulfadiazine are recommended by guidelines for preventative use. A variety of other measures have been studied, but are either recommended to be avoided or lack sufficient data to provide recommendations on use. Emerging therapies such as Alocane Plus may offer benefit in radiation dermatitis through its topical analgesic and antiseptic effects of lidocaine and benzalkonium chloride, respectively. In the absence of a gold standard algorithm for care of patients with or at risk for radiation dermatitis, clinicians should consider patients' risk factors, symptoms, and values and preferences in selecting a management approach.

ALOCANE® PLUS TOPICAL ANESTHETIC/ANTIMICROBIAL

TREATMENTS FOR EARLY STAGE WOUNDS, PRESSURE INJURIES, AND RADIATION DERMATITIS

Quest Products creates healthcare solutions for the way people live now: healing pain, providing relief and improving patients' quality of living. We use the most forward-thinking technology and ingredients to transform how providers can help patients approach their healthcare challenges

ABOUT ALOCANE® PLUS

ALOCANE® uses the most effective ingredients to numb, treat, and heal all types of early stage wounds.

4% LIDOCAINE Provides instant relief and stops pain on contact. 4% is the maximum OTC percentage allowed by the FDA. No other gel offers more without a prescription.

0.13% BENZALKONIUM CHLORIDE Provides antimicrobial benefit to help prevent infection and aid with anti-inflammatory, pain-relieving, and healing properties.

ALOE VERA Hydrates damaged skin, soothes irritation and cools burns. Aloe vera also contains antioxidant and antibacterial properties to keep first-degree burns protected from infections and inflammation.

VITAMIN E Naturally fights scars and accelerates healing for a wide range of first-degree burns and other injuries. Vitamin E also helps lighten and minimize scarring that can result from burns and scrapes.

Item #	ALC03243	ALC1168
Storage	With medical supplies such as antiseptics	Stored with first-aid supplies for convenient take home-treatment
Container	Small tube size, for mobility and convenience	Small single pouches for mobility and convenience
Size	2 oz tube filled with gel	48 count box of single use pouches
Case Count	48	12
NDC#	68229-300-03	68229-300-06
UPC #	8-46241-03243-7	8-46241-01168-5
ICD-10-Wound	Z48.00	Z48.00
ICD-10-Pressure Injury	L89-	L89-
ICD-10-Radiation Dermatitis	L58-	L58-
ICD-10-Venous Stasis Ulcer	I87.319	I87.319

Quest Healthcare is focused on medicines that change lives, pursues integrity and humanity, and strives to build a team that passionately pursues excellence. Quest Healthcare provides knowledgeable expertise to those facing life-altering illness or injury to reclaim their lives. In addition, Quest Healthcare provides an extensive network of information to assist healthcare providers in their pursuit to provide superior care for their patients and loved ones, as well as aide our patients in their journey to building a more independent life.

For sample requests and product information visit
www.questhealthcare.net/alocane

Or contact us at **customercare@questproductsinc.com** or **800-650-0113**

Quest Products LLC, Pleasant Prairie, WI 53158

QUEST HEALTHCARE

References

1. Hegedus F, Mathew LM, Schwartz RA. Radiation dermatitis: an overview. *Int J Dermatol.* 2017;56(9):909-914. doi:10.1111/ijd.13371
2. Singh M, Alavi A, Wong R, Akita S. Radiodermatitis: a review of our current understanding. *Am J Clin Dermatol*. 2016;17(3):277-292. doi:10.1007/s40257-016-0186-4
3. Delfino S, Brunetti B, Toto V, Persichetti P. Burn after breast reconstruction. *Burns*. 2008;34(6):873-877. doi:10.1016/j.burns.2007.11.004
4. Spalek M. Chronic radiation-induced dermatitis: challenges and solutions. *Clin Cosmet Investig Dermatol.* 2016;9:473-482. doi:10.2147/CCID.S94320
5. Tejwani A, Wu S, Jia Y, Agulnik M, Millender L, Lacouture ME. Increased risk of highgrade dermatologic toxicities with radiation plus epidermal growth factor receptor inhibitor therapy. *Cancer*. 2009;115(6):1286-1299. doi:10.1002/cncr.24120
6. Borrelli MR, Shen AH, Lee GK, Momeni A, Longaker MT, Wan DC. Radiation-induced skin fibrosis: pathogenesis, current treatment options, and emerging therapeutics. *Ann Plast Surg.* 2019;83(4S Suppl 1):S59-s64. doi:10.1097/sap.0000000000002098
7. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Cancer.gov. Published November 27, 2017. Accessed October 29, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
8. Zenda S, Ota Y, Tachibana H, et al. A prospective picture collection study for a grading atlas of radiation dermatitis for clinical trials in head-and-neck cancer patients. *J Radiat Res.* 2016;57(3):301-306. doi:10.1093/jrr/rrv092
9. Wolf JR, Hong AM. Radiation dermatitis. In: Post TW, ed. UpToDate. UpToDate; 2021. Accessed August 16, 2021. www.uptodate.com
10. Rosenthal A, Israilevich R, Moy R. Management of acute radiation dermatitis: a review of the literature and proposal for treatment algorithm. *J Am Acad Dermatol.* 2019;81(2):558-567. doi:10.1016/j.jaad.2019.02.047
11. Iacovelli NA, Torrente Y, Ciuffreda A, et al. Topical treatment of radiation-induced dermatitis: current issues and potential solutions. *Drugs Context*. 2020;9. doi:10.7573/dic.2020-4-7
12. Yang X, Ren H, Guo X, Hu C, Fu J. Radiation-induced skin injury: pathogenesis, treatment, and management. *Aging* (Albany NY). 2020;12(22):23379-23393. doi:10.18632/aging.103932
13. Wong RK, Bensadoun RJ, Boers-Doets CB, et al. Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Toxicity Study Group. *Support Care Cancer.* 2013;21(10):2933-2948. doi:10.1007/s00520-013-1896-2
14. Lucey P, Zouzias C, Franco L, Chennupati SK, Kalnicki S, McLellan BN. Practice patterns for the prophylaxis and treatment of acute radiation dermatitis in the United States. *Support Care Cancer.* 2017;25:2857-2862. doi:10.1007/s00520-017-3701-0
15. Hughes A, Mitchell AP, Bianchini J, et al. Symptom management guideline: radiation dermatitis. *BC Cancer Agency.* Published July 2012. Updated October 2013. Accessed November 1, 2021. http://www.bccancer.bc.ca/nursing-site/Documents/Symptom%20Management%20Guidelines/14RadiationDermatitis.pdf
16. Robijns J, Lodewijckx J, Mebis J. Photobiomodulation therapy for acute radiodermatitis. *Curr Opin Oncol.* 2019;31(4):291-298. doi:10.1097/cco.0000000000000511
17. Aguiar BRL, Guerra ENS, Normando AGC, Martins CC, Reis P, Ferreira EB. Effectiveness of photobiomodulation therapy in radiation dermatitis: A systematic review and meta-analysis. *Crit Rev Oncol Hematol.* 2021;162:103349. doi:10.1016/j.critrevonc.2021.103349
18. Robijns J, Lodewijckx J, Bensadoun RJ, Mebis J. A Narrative review on the use of photobiomodulation therapy for the prevention and management of acute radiodermatitis: proposed mechanisms, current clinical outcomes, and preliminary guidance for clinical studies. *Photobiomodul Photomed Laser Surg.* 2020;38(6):332-339. doi:10.1089/ photob.2019.4761
19. Alocane Plus. Package insert. Quest Products; 2021.
20. Hilal-Dandan R, Brunton LL. Local Anesthetics. In: Hilal-Dandan R, Brunton LL, eds. Goodman and Gilman's Manual of Pharmacology and Therapeutics. 2nd ed. McGraw-Hill Education; 2016. accesspharmacy.mhmedical.com/content.aspx?aid=1127549400
21. Treadwell T, Walker DL, Nicholson BJ, Taylor M, Alur H. Treatment of pain in wounds with a topical long acting lidocaine gel. *Chronic Wound Care Manage Res*. 2019;6:117-121.
22. Merchel Piovesan Pereira B, Tagkopoulos I. Benzalkonium Chlorides: Uses, Regulatory Status, and Microbial Resistance. *Appl Environ Microbiol.* 2019;85(13). doi:10.1128/AEM.00377-19
23. Weigelt MA, McNamara SA, Sanchez D, Hirt PA, Kirsner RS. Evidence-Based Review of Antibiofilm Agents for Wound Care. *Adv Wound Care* (New Rochelle). 2021;10(1):13-23. doi:10.1089/wound.2020.1193
24. Stoffel JJ, Kohler Riedi PL, Hadj Romdhane B. A multimodel regime for evaluating effectiveness of antimicrobial wound care products in microbial biofilms. Wound Repair Regen. 2020;28(4):438-447. doi:10.1111/wrr.12806
25. Cancer Care Manitoba. Part 4. Management of acute radiation-induced skin toxicities. Cancer Care Manitoba. Published January 2018. Accessed November 1, 2021. https://www.cancercare.mb.ca/export/sites/default/For-Health-Professionals/.galleries/files/treatment-guidelines-rro-files/practice-guidelines/supportive-care/Part_4_Management_of_Acute_Radiation-Induced_Skin_Toxicities.pdf