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COMMENTARY

Cutaneous Radiation Injuries: Models, Assessment and Treatments

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INTRODUCTION

Multiple cases of human exposure to radiation have been documented from the atomic bombings, nuclear power plant disasters and other industrial and medical accidents. Many of these exposures have led to pronounced cutaneous radiation injury (CRI), which played a significant role in the progression of damage and survivability of the radiation exposure and led to a lifetime of pain and scarring. Documentation of CRI from routine clinical radiotherapy and diagnostic procedures has also provided valuable information about the natural history of the injury. In response to the threat of a radiological or nuclear incident, the U.S. Department of Health and Human Services tasked the National Institute of Allergy and Infectious Diseases (NIAID) with identifying and funding early- to mid-stage medical countermeasure (MCM) development to treat radiation-induced injuries. Although there are now products to treat radiation-induced bone marrow damage, there are still no approved products specific for the treatment of CRI. To accurately assess severity of CRI and determine efficacy of different treatments, animal models must be developed that simulate what is seen in humans. It is also important to understand techniques used in other clinical indications to accurately assess the extent of skin injury and progression of healing. For these reasons, the NIAID partnered with the Food and Drug Administration (FDA)[2] and the Biomedical Advanced Research and Development Authority (BARDA) to identify state-of-the-art methods in assessment of skin injuries, explore animal models to better understand radiation-induced cutaneous damage and explore treatment approaches. A two-day workshop was convened in Rockville, MD on May 6 and 7, 2019, highlighting talks from 28 subject matter experts across five scientific sessions, and from this workshop a report was generated (*1*). This commentary provides a brief overview of the data presented at the workshop, and the key points that were considered during the discussion sessions that were held throughout the meeting. A more complete background and discussion of the workshop are available in the full report.

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BACKGROUND

Human Experiences with CRI and Other Skin Wounds

To provide a historical account of large-scale human radiation exposures, incidents involving CRI were discussed, which included the atomic bombings, where reports estimate that over 50% of the deaths were due to thermal burns (*2*), the Marshall Islands U.S. nuclear testing, where inhabitants were exposed to fallout contamination (*3*), and the Chernobyl Nuclear Power Plant accident, where 20 of the 22 fatalities within the first 14–34 days after exposure were mainly due to beta-burns (*4*). In addition to considering large-scale exposures, discussions also centered on treatment of patients who had sustained pronounced CRI from industrial accidents. Many of these individuals were treated at the Hôpital d'Instruction des Armées Percy in Paris, France, with input from radiation experts at the Institute for Radiological Protection and Nuclear Safety (IRSN; Fontenay-aux-Roses, France). IRSN has pioneered multiple treatment methods and is working toward global harmonization of diagnosis and treatment to address CRI in humans. Highlighting treatments and outcomes for several CRI cases, it was emphasized that radiation-induced skin complications are complex and chronic pain can persist. Radiation burns evolve over time in successive inflammatory waves, making prognosis difficult, and there is also a lag time in wound healing that can result in wounds that close, but re-develop into lesions over time.

Another source of human CRI cases involves those resulting from radiotherapy, which continue to be a clinical problem despite technological advances in cancer treatments. Radiation dermatitis has been documented as one of the most prevalent acute toxicities in radiotherapy patients (*5*). Standard medical management for radiation dermatitis

could be relevant to treatment options for cutaneous radiation injury; however, there is little consensus on which topical agents effectively alleviate symptoms, although a few approaches have been studied (*6–11*). In addition to a consideration of radiation-induced skin wounds, presenters discussed cutting-edge technologies to assess and treat skin injuries resulting from other types of damage and disease states. For example, stem cell spray devices have shown potential for thermal burns, and case studies describing the use of spray grafting technology have been reported (*12*). Further informing an understanding of treating radiation skin injuries are chronic wounds resulting from disease states, such as diabetic foot ulcers. A number of underlying factors in the progression of diabetic foot complications, such as poor blood flow, structural imbalance and infection, lead to a failure of these wounds to heal. Likewise, radiation is known to cause macrovascular disruption through activation of cytokines and recruitment of inflammatory cells. In summary, there is a wealth of experience that can be accessed from both the human radiation experience of accidental and clinical exposures, as well as from existing practice of medicine for other types of skin injuries to help guide the selection of the best approaches to address CRI.

Preclinical Models of CRI

The data from human exposures have limitations in terms of confirming radiation dose received and how natural human variabilities influence response. Animal and *in vitro* human skin models, before however, represent a means of studying radiation skin injury that can be closely monitored and are more uniform. There are a number of different strategies to produce CRI. Radiation skin injuries in Göttingen minipigs[3] were produced using a Grenz device, which delivers a superficial surface dose, depositing most of its energy in the outer layers of the skin. CRI can also be created using an X-ray machine, which possesses higher energy, and elicits less damage on the skin surface but more severe damage deeper within the skin layers. Beta particles, which would be the biggest concern in a fallout exposure, may also be used.

A murine model has been developed in which a full-thickness incision is made to the skin and then allowed to heal. In this model, wound tensile strength (WTS) is a reliable means of measuring the strength of healing of the wound in the presence or absence of radiation and MCM treatments (*13*). Determining the extent of skin injuries is integral to another mouse model for radiation combined injury (RCI) that involves both radiation exposure and another trauma (*14*). This model is important for study, because the Hiroshima and Nagasaki bombings resulted in 39–42% of the injuries documented as RCI (*15*). In animal models of burns or wounds delivered 1 h after total-body irradiation, combined injuries reduced survival (*16*) and delayed wound healing. In search of an animal model that is physiologically closer to human skin than small rodents, researchers have turned to pig models. Investigators have developed a guinea pig model for CRI to test efficacy of products (*17*). The guinea pig simulates human physiology and response to CRI (*18, 19*). In large animal model development, CRI in the Göttingen minipig strain has also been modeled on a human radiation accident involving skin injuries (*20*). A combination of scoring, imaging, histology and other novel methods (e.g., planimetry, color image analysis, ultrasound, thermography, MRI, etc.) were employed. Development of this model has established end points that may be applicable to assessing the severity of skin injury and studying the efficacy of MCMs to mitigate CRI. Finally, Yorkshire pigs have also been used to study CRI. They are well characterized in terms of the similarity of their skin to humans (*21, 22*) and are frequently used for drug testing of many dermatologic indications. The Yorkshire pig has also been developed as a model to demonstrate improvements in skin healing with MCM administration after exposure to a beta radiation source (*23, 24*).

In developing and using preclinical models of CRI, researchers should consider ethical challenges, such as identifying and addressing animal pain. There are also standard clinical practices involved in the care of wounds that could be translated into animal models, such as debridement and antimicrobial therapy. Other important considerations include the heterogeneity of humans and animals and its influence on radiation dose distribution [e.g., subcutaneous skin thickness and body fat, healing rates that vary based on what part of the skin is irradiated, proximity to bone and effect of skin melanization (*25*)]. Gaps in knowledge derived from animal studies may also be bridged by using alternative human skin models. Advances in tissue engineering have provided models for the study of the human skin radiation response including cell lines, organoids, full-thickness skin, tissue chips, 2-D and 3-D models, and dermal equivalents. As with *in vivo* models, the goal of these alternatives is to more closely simulate human skin, minimize animal use, and allow for less expensive screening of potential MCMs (*26–28*).

Assessing CRI

In determining the efficacy of a treatment, consideration must be given regarding how the wound and any healing will be evaluated; however, there is no current consensus on this in the research or clinical communities. Methodologies beyond visual assessment that may be useful in determining the extent of injury and progression of healing include ultrasound, infrared imaging, optical coherent tomography, laser doppler, thermography CT scans and MRI imaging. Clinical scoring scales with histopathology can also be used to make assessments more quantitative and objective. To

[3] Lovelace Biomedical Medical Countermeasures; https://bit.ly/3dXxc65.

more clearly evaluate the degree of CRI, a number of scoring systems were discussed that have been used both clinically and pre-clinically to assess the severity of different kinds of skin injuries. These include the NIH Common Terminology Criteria for Adverse Events (CTCAE) (*5*), the Kumar scale (*29*), the Radiation Therapy Oncology Group (RTOG®) Clinical Assessment System (*30*), Wound Ischemia and foot Infection (WIfI) (*31*) and others. In addition to other scoring systems in use to assess skin injuries, METREPOL (MEdical TREatment ProtocOLs for Radiation Accident Victims) grading, which includes scoring for other radiation injuries as well as skin, can be helpful to determine course of treatment for irradiated patients (*32*).

Regulatory Considerations for Products to Address CRI

The safety of MCM products designed to counter radiological threats is evaluated in healthy volunteers; however, where human efficacy studies of MCMs are unethical or not feasible, the ''Animal Rule'' allows the FDA to grant approval of new drugs or biologics based on efficacy studies in animals, provided that such studies are well controlled and establish the MCM product as reasonably likely to provide clinical benefit in humans (*33*). Efficacy of a product should be demonstrated in more than one animal species; however, it is not necessarily rodent and non-rodent. Natural history studies should establish a reproducible injury model with well characterized documentation of the depth and area of the wound based on histological verification. For clinical studies, complete wound closure is a clinically meaningful wound healing end point (*34*). Desired clinical outcomes in CRI may also include improved survival and healing or ability to achieve durable skin coverage of the wound. Histopathology is considered the gold standard for characterizing CRI, so to assess wound severity, modalities to consider may include clinical, planimetry, thermography, histopathology and ultrasound. Dressing devices intended for severe CRI may not be appropriate for 510(k) review; depending on the claims and mechanism of action, other regulatory paths may be appropriate. Note that the Animal Rule does not apply to devices, as it may be acceptable not to have clinical data in hand for some marketed devices. Regulatory guidance from the FDA should be sought early, so that resources are not wasted in developing models that would not be acceptable to the agency.

CRI Treatments

One of several promising approaches to treat CRI is cellular therapy. Stem cells used for treatment may originate from different sources such as the bone marrow, blood or other tissues. Percy Military Hospital has performed stem cell therapy in human patients (*35*), documenting complete healing of radiological burns with functional recovery and rapid loss of pain. Another approach involves repurposing of Silverlon® burn contact dressings, which are currently cleared for the management of a wide variety of wounds. There are also products that target skin structural components such as KeraStat® Cream (containing purified, human-derived keratin), which have been studied to manage porcine and human skin injuries. FirstString Research (Mount Pleasant, SC) is focused on developing a topical skin treatment, Granexin® gel (aCT1 peptide), that has demonstrated activity in non-clinical and clinical studies (*36*). The aCT1 peptide is intended to temper damaging inflammatory responses and intended to help preserve and restore the coordinated cellular activity that is compromised after injury. Studies of severe radiation-induced skin ulcerations in the previously cited guinea pig model showed activity of USB001, an angiotensin analog developed by US Biotest (San Luis Obispo, CA), when the product was applied at either the start of erythema or loss of dermal integrity (*17*). Finally, Chrysalis BioTherapeutics (Galveston, TX) has developed novel thrombin peptide regenerative drugs to address skin injuries. The company's TP508 product has demonstrated safety and activity in human clinical trials for diabetic foot ulcers (*37*), and efficacy in an RCI mouse model.

CONCLUSIONS

To address cutaneous radiation injury, a team approach is needed that includes trauma clinicians, radiation oncologists, radiation physicists, and dermatologists. More rapid and accurate diagnoses and better assessment regarding the depth, breadth and severity of injury, including blood supply, is needed to better understand the extent of injury. Animal modeling requires a link to human skin injury that can be observed with the use of imaging, such as ultrasonography, thermography or MRI. As for treatment, it is not reasonable to expect that a single product will be able to address the heterogeneity of injury observed after radiation exposure of the skin. Additionally, standardization of methods to assess severity and treatment efficacy is needed. It is promising that several repurposed MCMs and drugs, for which clinical data are being gathered for another indication, are undergoing testing for CRI; this could accelerate the clearance/approval/licensure of these products. It is important that CRI research and development continue to receive support by funding agencies, and that CRI receives increased recognition as a key issue when discussing injuries anticipated from a radiation incident.

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