Chapter

Treatment Toxicity: Radiation

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Abstract

Radiation exposures, both intentional and unintentional, have influence on normal tissue function. Short-term and long-term injuries can occur to all cell systems of both limited and rapid self-renewal potential. Radiation effects can last a lifetime for a patient and can produce complications for all organs and systems. Often invisible at the time of exposure, the fingerprints for cell damage can appear at any timepoint after. Health-care providers will need comprehensive knowledge and understanding of the acute and late effects of radiation exposure and how these interrelate with immediate and long-term care.

Keywords: radiation exposure, cell damage, toxicity, radiation dose/volume

1. Introduction

Radiation exposure can occur during diagnosis and primary treatment of a cancer or during a nuclear incident. These exposures increase our need to educate health-care providers and first responders on assessing and managing patients [1–8]. Although effects on tissue may not be meaningful from a clinical perspective during an evaluation for healthcare, identification of radiation exposure from a dose and volume perspective is an important piece in the patient's past medical history. Invisible fingerprints relevant to medical situations can declare themselves decades after exposure in spite of careful periodic evaluation. The dose and volume of the intentional exposure is usually well documented in the radiation therapy treatment record. Shadow parallel radiation records that are not entered into electronic health system records may not be available at the time of a related health-care evaluation, and important clinical information may be too brief or inadequate. Many current electronic medical records (EMR) do not have a module for radiation oncology. Data acquisition and management of radiation oncology are conducted with proprietary software systems and are not directly included in the modern electronic record. Interfaces can be built to move small portions of records to the EMR; however these are not reliable modes of data transfer and, if transferred, often cannot be easily retrieved when needed in the acute care setting. Unintentional exposure including exposure from diagnostic imaging is more challenging to document as it is provider-dependent and limited reliable information is documented during a radiology procedure. Radiation dose exposure is estimated using distance and duration models from the primary source as victims, unlike health-care providers, are

frequently unmonitored [1–4, 6, 8]. While these estimation models may be useful, accuracy can be compromised, particularly in calculating the integral or total body dose as there are often multiple sources of radiation at the time of the unintended exposure along with thermal injury. With the increasing rate of cancer survivors and the transition of pediatric patients to adult care systems, there is a multilevel knowledge gap of the toxicities caused by radiation exposure and how the acute and late effects relate to patient care.

2. Radiation toxicity

2.1 Normal tissue damage

We arbitrarily categorize radiation injury into phases: acute injury (3 months from exposure), subacute (from 3 to 24 months from exposure), and late or chronic (>24 months from exposure). There is considerable overlap in these definitions, and acute injury can be less and non-predictive of chronic injury [1–4]. Acute intentional injuries, both expected and unanticipated, related to radiation therapy management of cancer are best managed by the responsible treating physicians during radiation treatment. These professionals are cognizant of the intended target and normal tissues in the treatment field. Their knowledge of radiation treatment's impact on normal tissue is coupled with established and less well-established toxicities with various applications of chemotherapy and targeted therapy. Unintentional radiation exposure requires additional support and evaluation by emergency services working together with radiation safety experts, who are trained in managing radiation effects and assessing the dose received by the victims using models of time and distance from the epicenter of the event. This also includes evaluating the risk to caregivers of the victim if radioactive particles/elements remain on or in the victim. The acute phase of injury can affect many cell systems. This includes toxicity to limited and rapid self-renewal potential tissues such as the central nervous system, bone marrow, skin, and mucosal surfaces lining the head/neck and gastrointestinal system. Death can occur soon after exposure if it is not recognized in a timely manner and appropriate support is not provided. Although injury to reticulum systems is less common from radiation exposure due to limited self-renewal of these cell systems, injury to these systems including thermal injury eliminate the scaffolding needed for structural repair of cell systems with rapid self-renewal potential as disorderly repair can severely limit cell function.

From an individual cellular perspective, radiation therapy has direct impact on intracellular molecules and can cause both single-strand and double-strand DNA breaks which are repaired through multiple mechanisms. Because water is an important intracellular compound, oxygen compounds including free radical formation creates injury to cells through ionization from radiation exposure. These processes are important for cells and groups of cells near each other. The significance of the injury is directly related to the volume of tissue injured from the exposure as well as the degree of injury to support cells (stroma) that often have a more limited self-renewal capacity. If stroma is significantly damaged, cells with rapid self-renewal potential will not have a support architecture to reorganize and maintain function. The seriousness of acute and late injury is also proportional to the dose and volume of tissue exposed. Late injury is manifested by accelerated fibrosis coupled with limited blood vessel proliferation. The mechanism of late injury is multifactorial in origin including damage to rapid and limited self-renewal potential tissues, blood vessels, and intrinsic repair capacity of the cell system injured mitigated by mechanisms that accelerate fibrosis including TGF beta [9].

Radiation exposure symptoms differ with the severity of the exposure. At very high single-fraction total body doses (>10 Gy (Gray)), near-immediate death will occur through cerebrovascular syndrome despite medical care. The syndrome is due to profound edema within the brain and meninges associated with collapse of all neuromuscular processes due to swelling and herniation of the brain through the foramen magnum. At total body doses of 5–12 Gy, death without support will occur within a few weeks as a result of profound fluid loss and diarrhea due to denudation and destruction of the gastrointestinal system. This can affect both stem cells and cause secondary injury to subdermal structures deforming the architecture of the bowel inhibiting absorption and promoting fluid loss. Patient survival is directly correlated with gastrointestinal (fluid/nutrition) and bone marrow (blood/blood product) support during this phase after exposure. A single total body dose of 10 Gy will eradicate a large segment of the stem cells within the gastrointestinal crypts. Although this dose does not directly affect differentiated adult cells, the exposure eliminates the stem cell self-renewal potential; therefore, the gastrointestinal tract mucosal surface becomes denuded, and the reticulum architecture supporting cell organization can be damaged. As a result, with no barrier for fluid and blood loss, clinical deterioration will occur often within days. At total body exposure doses of 2–5 Gy, death occurs from destruction to the hematopoietic system with primary damage to both stem cells and cells of established lineation. Cells cannot sustain self-renewal, and clinical deterioration can occur with primary marrow failure and secondary infection. Lymphocytes may die an intermitotic death; thus the degree of lymphopenia can provide indirect assessment of dose from exposure [1, 5–8].

During exposure, symptoms consistent with a radiation syndrome will be developed by the victim and can be seen as early as 15 minutes from the initial exposure [1, 6, 8]. Symptom severity is proportional to dose. At higher doses, victims can experience severe gastrointestinal fluid loss, secondary fever from exposure to homeopathic pathogens, and hypotension due to fluid loss suggesting significant toxicity. Often identified at lower dose exposure, the prodromal phase is followed by a latent interval during which the person may look and feel clinically well for days to weeks. After this gastrointestinal and hematopoietic damage may become visible and require intervention to prevent further acute clinical deterioration [1, 5–8].

If the total body exposure is <4–5 Gy, most experts currently recommend no immediate intervention other than symptomatic treatment with fluids and blood support. This would include periodic hydration and antiemetic therapy for nausea and vomiting. As needed, infection can be treated with antibiotics. Death associated with the hematopoietic syndrome becomes a real concern for exposure >5 Gy. Barrier nursing intervention and appropriate blood product support may improve survival. Experience from recent nuclear events suggest that efforts to limit bleeding, infection, and physical trauma during the blood count nadir may improve the LD 50/30 (50% survival at 30 days) to and possibly beyond 7 Gy.

Dermal surfaces can receive much higher doses than internal organs, particularly if the exposure is related to particles. Dermal injuries can be primitive dose biomarkers with epilation/erythema at 3–6 Gy and wet desquamation, bullae, ulceration, and necrosis visible at increased doses [1, 10]. However, if the exposure is a contaminate of radioactive particle and photon exposure, dermal dose may not be an accurate assessment of total body dose. Dermal injuries can be life-threatening due to concurrent infection. Injuries should be managed with the same care offered to burn victims with care taken to monitor health-care staff in case there are residual particles which can transmit unintentional dose to health-care providers. Residual exposure can be identified with careful monitoring with dosimeters as done in brachytherapy treatments for health-care providers.

An accurate assessment of dose is very important during the triage and care of victims with unintended exposure. Health-care workers are often monitored with dosimeters; however, the public will not have access to these tools. Therefore, radiation exposure and dose assessment experts are important early in the evaluation including analysis of the population at risk. As radiation dose increases, the time to emesis decreases, and rapid onset of nausea and vomiting suggests higher exposure. As indicated, a decline in lymphocyte count or abnormal lymphocyte cytogenetics can be an indirect estimate of dose within 1–2 days of exposure. [1, 6–8, 11]. The Radiation Emergency Assistance Center for the United States (US) Department of Energy is operated by Oak Ridge Institute for Science and Education. Medical and radiation safety support is available through a 24-hour consultation service. Resources include radiation dose assessment in laboratory facilities and computation of dose from radionucleotide expertise. The 24-hour emergency telephone number is 865.576.3131, and the website is https://orise.orau.gov/reacts/resources/index.html.

Recognized as an important clinical endeavor since nuclear weapons have been developed, there is keen interest in finding the chemical compounds that can protect normal tissues against radiation injury. Radiation protectors are compounds applied or administered prior to exposure or in selected circumstances soon thereafter, to limit the impact and subsequent damage from exposure upon normal tissue. Compounds that can influence and promote the health of normal tissue after exposure are referred to as radiation mitigators. These therapeutic compounds are applied once the injury has occurred. Sulfhydryl compounds (SHs) have been shown to be effective radioprotectors. The simplest of these compounds, cysteine, contains a natural amino acid [11, 12]. The mechanism is thought to be related to the augmentation of amino acids in generating repair proteins at a higher level. Once the compound becomes intracellular, it loses the phosphate group and is thought to also serve as a free radical scavenger limiting intracellular damage.

Amifostine (ethyol) has been used to prevent xerostomia in patients receiving radiation therapy for head and neck cancer [13]. Several clinical trials have used amifostine to evaluate the effectiveness in protecting multiple mucosal surfaces as well as protecting pulmonary injury in patients undergoing total body irradiation therapy as part of bone marrow transplant [13]. Amifostine was associated with improvement in patient assessment of mouth dryness and swallowing in a trial managed by the National Clinical Trial Network [13, 14]. The intrinsic fear of applying radiation protectors and mitigators in cancer therapy is the possible simultaneous tumor protective effect of these compounds in situ potentially limiting the usefulness of the compounds. In this trial, it is important to note there was no difference in tumor control between patients receiving amifostine and patients receiving placebo. Nitroxides have been identified by Citrin and colleagues [11] as radioprotection agents in clinical development. Stable nitroxide free radicals and their specific electron reduction products, hydroxylamines, protect cells when exposed to oxidative stress. Accordingly, similar compounds are under review and evaluation. Antioxidants, such as alpha-tocopherol and beta-carotene, are under review for clinical application but to date have not been shown to be of clinical benefit [15, 16]. Investigators explored using gene therapy vectors with superoxide dismutase (SOD) to improve the intracellular component of SOD. The purpose is to limit damage caused by superoxide radicals. Investigators have demonstrated improved normal tissue tolerance to multiple organs including the esophagus with this approach [17, 18]. Captopril is a sulfhydryl containing analog of proline and inhibits angiotensin-converting enzyme and limits vasoconstriction. In animal models, it has been shown to benefit renal and pulmonary function with total body irradiation by limiting endothelial dysfunction, fluid exudation, and the subsequent development of pulmonary fibrosis. It also appeared to improve recovery

of hematoprogenitor cells [19–21]. ON 01210 (chlorobenzylsulfone derivative) is a small molecule kinase inhibitor which potentiates recovery of peripheral blood elements when administered before radiation. This may be of benefit to the general public and first responders in an unanticipated event if received early postexposure [22]. Animal models have shown a positive repopulation effect of gastrointestinal stem cells with R-spondin 1, a 263 amino acid protein [23]. CBLB502 is an agent that binds to toll-like receptor 5 (TLR5) activating NF-kB signal pathways. It is derived from the flagellin protein of *Salmonella* bacteria. It promotes recovery and regeneration of multiple organ system stem cells after TBI therapy including GI, oral mucosa, skin, and bone marrow progenitors. IL-6 and other bone marrow-associated colony-stimulating factors likewise appear to work in parallel with this compound. The compound has a potential role as both a protectant and a mitigator [24]. Gamma-tocotrienol is an isomer of vitamin E and supports survival in animal models during total body irradiation in part by promoting bone marrow colony-stimulating factors and IL-6. It also may play a role in upregulating anti-apoptotic gene expression after radiation [25, 26].

The role of mitigators is to limit injury from radiation exposure prior to the clinical manifestations of acute and late toxicities of the exposure and treatment. These compounds are generally thought to influence metabolic events occurring after exposure and limit radiation-associated damage. To date, cytokines and growth factors directed to stimulate stem cell proliferation are the most common tools used for this purpose. In clinical practice, these are commonly used to balance the inhibition of stem cell growth induced by chemotherapy and radiation to the hematopoietic, dermal, and gastrointestinal systems. These include granulocyte colony-stimulating factor (G-CSF) and keratinocyte growth factor (KGF) [27]. The factors contribute to many aspects of cell recovery. KGF has positive influence in the recovery of mucosal surfaces during the acute phase of toxicity as well as limits the late effects of radiotherapy, including xerostomia [11]. This is thought to potentially be of benefit to patients undergoing primary management for head and neck tumors. Mitigators of late toxicity are largely directed to limit fibrosis, which is thought to be a primary factor in late pulmonary injury and other tissues of more limited self-renewal potential [11, 15–18, 28–32]. Transforming growth factor beta (TGF-B) is the primary target to limit fibrosis [33–35]. Several compounds in development prevent late effects to either directly or indirectly target the TGF-B signaling pathway [33–35]. Tumor protection remains a concern when evaluating treatments associated with this parallel pathway for patients being treated for a malignancy, identical to compounds associated with radiation protection. There has been increasing interest in the use of stem cell therapy to repair both acute and chronic injuries. Mesenchymal stem cells modified with extracellular superoxide dismutase have been shown to improve survival of irradiated mice [36]. There is evidence these progenitors have a pleuripotent role and can be called upon by organ systems for differentiation along multiple pathways. Bone marrow stromal cells and myeloid progenitors are also under evaluation to mitigate radiation response. The survival benefit in mice with infusion of myeloid progenitors could be seen days after exposure [37–40]. The role of these infusional therapies in this circumstance remains to be optimally defined. The role of transplant and stem cell infusion during the Chernobyl crisis was uncertain; however these techniques have improved and remain to be optimized in similar situations moving forward.

Neutrophil inhibition has the potential of limiting the severity of response to injury, and this has been evaluated in a series of experiments determining the potential role of these strategic compounds applied after radiation exposure. Experiments evaluated interleukin-1 alpha (IL-1α) as a mitigator of dermal damage after radiation exposure. Interleukin-1 (IL-1) inhibits neutrophil infiltration

into the initial inflammatory response to injury. Assuming the initial inflammatory phase can be titrated, short-term and long-term injuries could be influenced. Knockout mice deficient in IL-1α or the IL-1 receptor demonstrated both decreased dermal injury and more rapid healing after superficial radiation exposure with both electrons and a strontium applicator. This demonstrated the potential importance of this cytokine in generating and ameliorating radiation-associated skin damage associated with neutrophil inhibition. In a separate group of experiments, investigators demonstrated that hyperspectral optical imaging (HSI) can reveal acute and late oxygenation and perfusion changes in dermal tissue with changes occurring as early as 12 hours after radiation exposure [41, 42]. Imaging changes in oxygenation and perfusion were seen within 12 hours of exposure and predated clinical visible skin change by 14 days [42]. Data sets from this group as part of an approved Institutional Review Board clinical trial for breast cancer patients receiving radiation therapy have shown that changes in imaging correlate well with radiation dose and dose asymmetry in the treated volume. Areas of increased dose associated with patient topography, and chest wall separation demonstrated changes consistent with increased dose and daily fractionation.

In response to the need of developing compounds for radioprotection and mitigation, the Radiation Research Program of the National Cancer Institute in collaboration with the Small Business Innovation Research program has funded a series of contracts since 2010 to support the development of radiomodulators. To date, five of the funded applications have successfully transitioned to phase II funding. Eight clinical trials have been developed to establish safety and efficacy. Two drugs on trial are under evaluation as radioprotectors, and two are also being evaluated for anticancer properties. The sites of interest being studied include CNS injury, mucositis, proctitis/enteritis, bone marrow failure, and lung injury [43].

3. Conclusions

Researchers are developing a targeted pharmacologic response to protect and mitigate issues surrounding intentional and unintentional radiation exposure. A knowledge of normal tissue response to radiation injury will be important for all health-care providers moving forward. Radiation therapy patients, accident victims, and first responders will benefit from the growing body of knowledge.

Conflict of interest

The authors have no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.88192

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