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Acute Radiation Syndrome at Crossroads of Protection and Therapy

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Abstract

Exposure to radiation (>1Gy) induced acute radiation syndrome (ARS), reducing individual defense against exogenous and endogenous factors, resulting in infections and organs dysfunction. Since < 40% of cancer patients require radiation therapy for management, developing acute radiation toxicity, manifesting during or developing months to years after completion. The development of radiation countermeasure to treat ARS patient has been the subject of intense research since World War II. Individual radiation toxicity is assessed by the time gap of onset, severity of nausea and vomiting, and decline in absolute lymphocyte count, over several hours or days after exposure. Numerous synthetic and natural products though evaluated, however, unwanted toxicity even with optimal doses has precluded their usage. Therefore, systematic screening approach is recommended to identify potential new drugs for mitigation of radiation injury. Sincere efforts have been put in the current review to process preclinical to clinical trials, FDA approved treatment modalities and drugs. Therapy includes treatment with hematopoietic cytokines; blood transfusion; and, stem-cell transplantation, in selected cases. Discussions on medical management, of presenting clinical symptoms and signs, envisage the use of radiomimetic, immune-modulatory and anti-inflammatory agents.

Keywords: Radioprotection, Radiomitigation, Radiation Injury, Acute Radiation Syndrome, Stem cell Therapy.

1. Introduction

Ionizing radiation can be due to electromagnetic (such as gamma rays or X-rays) or particle radiation (such as neutron or alpha particle) resulting in ionization of atom or molecules. Although ionizing radiation is considered hazardous by the general public, it finds application in many therapeutic, industrial (generation of nuclear power), agricultural (developing new varieties of high yielding crops and enhancing storage period of food materials). There are two types of exposure to ionizing radiation: planned exposures and unplanned exposure. Major planned exposures are Radiotherapy of cancer, diagnostic exposure, nuclear industry and space programme. While nuclear accidents, nuclear emergencies, nuclear warfare and nuclear terrorism are of unplanned exposure. Further, planned exposures are of two types: external and internal radiation exposure. Two main types of external irradiation are Gamma and X-rays, whereas internal radiations are caused by localization of radionuclide in critical organs.

The deleterious effects of ionizing radiation at cellular levels are attributed to the direct deposition of energy, and indirectly through the generation of highly reactive free radicals, mainly reactive oxygen species (ROS) [1]. DNA is the primary and membrane the secondary target. Effect of radiation is due to absorption of energy directly by DNA, leading to ionization of the nitrogenous bases and sugar, generating singular or multiple DNA damage. The damage from this insult is irreparable, and cell either dies or malfunctions. Indirect effect of ionizing radiation is

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known to account for approximately 75% of the damage to cells [2]. ROS are formed by radiolysis of water and cause extensive cellular damage such as- nucleic acid strand scission, modification of polypeptides, and lipid per oxidation. These damages are not nullified, lead to affectation of the cell structure and function, resulting in tissue damage- reproductive death, interphase death, division delay, chromosome aberrations, mutations and transformations, ultimately leading to cell death by necrosis and apoptosis or to neoplastic transformation.

2. Acute Radiation Syndrome

Exposure to high amount of ionizing radiation results in damages to various organs of the hematopoietic, gastrointestinal or central nervous system, resulting in radiation toxicity or radiation sickness or acute radiation syndrome (ARS). ARS as defined by the Centres for Disease Control and Prevention is "an acute illness caused by irradiation of the entire or most of the body, by a high dose of penetrating radiation in a matter of minutes."[3].

ARS is rare but is potentially fatal on total or partial body exposure to relatively high level of radiation (approximately 1Gy or more) over relatively short time frame. The nature and severity, depend on (a) Dose; (b) dose rate; (c) dose distribution; and (d) individual susceptibility. Dosages of Whole-body radiation can be divided into potentially lethal (2–10 Gy), sublethal (<2 Gy) and supralethal (>10 Gy). Whole-body exposure to external penetrating radiation can have both immediate and late effects. The required conditions for development of ARS include:

- Large dose of radiation
- External source of radiation
- Radiation must be penetrating
  All or most of the body must have received the dose
- The dose must be delivered in a short time, usually a matter of minutes

Events associated with a risk of acute radiation syndrome include explosion of an atomic bomb, nuclear accident or unintentional exposure to sterilization irradiators. Well-known examples of such catastrophic situations include the nuclear reactor meltdowns at Three Mile Island and Chernobyl.

Acute radiation syndrome has four clinical stages: prodromal, latent, illness manifestation and recovery/death. The prodromal stage is characterized by symptoms which are dose-dependent- nausea, vomiting and diarrhoea. Nausea is unpleasant sensation of uueasiness or stomach upset, precedes or accompanies the act of vomiting. Symptoms may begin just minutes after exposure, with episodes typically lasting no more than 48 hours. During the latent stage, which can last from a few hours to a few weeks, the individual may feel and appear to be healthy. However, as a result of bone marrow insult, cell populations of leukocytes and platelets, undergo critical depletion during this stage. The duration of latency decreases as the radiation dose increases. During the stage of manifest illness, symptoms of overt illness emerge and last for weeks or months. This stage is characterized by symptoms of intense immunosuppression, depending upon the radiation dose, system affected-bone marrow, gastrointestinal or neurovascular, as well as factors such as age and underlying health status. During the fourth and final clinical stage, the patient may recover; or will die within months of exposure. The chance of survival decreases with increasing radiation dose [4, 5].

3. Pathogenesis of Acute Radiation Syndrome

Rapidly dividing cells are most susceptible to the injurious effects of ionizing radiation [5, 6]. Depending upon organ system(s) affected-bone marrow, gastrointestinal or neurovascular, symptoms of ARS syndromes are present during the manifest illness stage. In a patient exposed to whole-body or partial irradiation at doses of 1 Gy or higher, irradiation of bone marrow stem cells and progenitor cells triggers exponential cellular death and manifests as hematopoietic syndrome. Hematologic crisis (hypoplasia or aplasia of the bone marrow) occurs within weeks of exposure, resulting in bleeding, pancytopenia, poor wound healing, impaired immunity and predisposition to infection and sepsis, all of which contribute to negative prognosis [4, 5].

In a patient exposed to whole-body or partial irradiation at doses of 6–10 Gy, radiation-induced loss of the intestinal endothelium crypts and breakdown of the mucosal barrier results in gastrointestinal syndrome, characterized by pathological damage to the gastrointestinal tract;. Symptoms include abdominal pain, severe diarrhoea, nausea and vomiting, high fever and predisposition to infection. Systemic effects of the gastrointestinal syndrome include malnutrition, electrolyte imbalance secondary to malabsorption, bowel obstruction from ileus onwards, dehydration,

Table 1. Consequences of radiation exposure

S.N.	Radiation Dose	Effect of Radiation Exposure
1	50–100 mSv	Changes in blood chemistry
2	500 mSv	Nausea, within hours
3	700 mSv	Vomiting
4	750 mSv	Hair loss, within 2–3 weeks
5	900 mSv	Diarrhoea
6	1000 mSv	Hemorrhage
7	4000 mSv	Possible death within 2 months, if no treatment.
8	10,000 mSv	Destruction of intestinal lining, internal bleeding and death within 1–2 weeks.
9	20,000 mSv	Damage to the central nervous system and loss of consciousness within minutes, and death within hours or days.

Source: US Environmental Protection Agency (http://epa.gov/radiation/understand/health_effects.html).

anemia, gastrointestinal bleeding, sepsis, acute renal failure and the bone marrow affectations.. The mortality rate in this syndrome is extremely high [4,5].

The least well-defined and most rapidly progressing syndrome is cerebrovascular syndrome, symptoms of which are observed in individuals receiving a radiation dose of 20 Gy or higher. The prodromal stage is characterized by confusion/disorientation, loss of balance and seizures. Manifest illness is severe, with symptoms including watery diarrhoea, respiratory distress, hyperpyrexia and cardiovascular shock. Circulatory complications include hypotension, cerebral edema, elevated intracranial pressure and cerebral anoxia. Death usually occurs within two to three days [4].

Cutaneous syndrome, which has been described more recently than the other three ARS, results from thermal or radiation burns and loss of dermis. Injuries may show affectation of small superficial areas of the skin, but found to extend deeply into soft tissue, underlying muscle and/or bone [4], thereby affecting cell-to-cell communication and resulting in break down of cutaneous integrity [7]. Symptoms include erythema, edema, itching or swelling, blistering, desquamation, ulceration or necrosis, hair loss and onycholysis. The disease course is more complicated in patients with concurrent hematopoietic syndrome, with its characteristic abnormalities of bleeding, infection and wound healing [4]. In summary, the following can be anticipated in an exposure to levels specified in the Table 1.d to short-term, high-level doses of radiation.

A related condition, termed radiation combined injury (RCI), occurs when a subject with acute radiation syndrome also suffers from additional severe injuries including burns, wounds, trauma and/or sepsis. Prognosis in patients with RCI is significantly worse. Radiation combined injury is most often associated with the detonation of a nuclear weapon, such as the nuclear attacks on Hiroshima and Nagasaki during World War II.

4. Diagnosis of Acute Radiation Syndrome

The diagnosis of acute radiation syndrome without a confirmed history of acute exposure to ionizing radiation can be rendered difficult, by the nonspecific nature of symptoms [5]. A complete blood count should be initially collected and repeated regularly (every 4 hours for the first 8 hours, then every 6 hours for the following 40–48 hours), while measuring the absolute lymphocyte count. An initially low or rapidly falling lymphocyte count is indicative of a high dose of radiation [5]. Estimation of exposure is important as it is needed to guide therapy decisions [8].

Information about estimated radiation dose and severity of radiation illness can also be inferred on the basis of time to onset of vomiting, which is typically inversely related to absorbed dose. However at lower doses this information is less reliable. An estimated dose of 8 Gy or higher the onset of vomiting ranges from <10 minutes. At doses of <2 Gy4 vomiting manifests >2 hours or may be absent. As emesis is symptomatic of a range of other conditions, patients should also be assessed for other adverse health effects, before a diagnosis of acute radiation syndrome [8].

Cytogenetic dosimetry is the gold standard and only accurate method of determining radiation dosing. The test is based on predictable and standardized effects of radiation on the replication of DNA in lymphocytes. However, cytogenetic dosimetry is not widely available and results take several days to process [5, 8].

5. Treatment of Acute Radiation Syndrome

The treatment of patients presenting with acute radiation syndrome depends upon various factors including estimated radiologic dose, exposure scenario and presenting symptoms [4]. Radioprotectors are agents which

protect individuals against ill-effect of radiation. The terms 'prophylactic', 'mitigation', and 'therapeutic' are used to describe radiation-protective agents or radiation countermeasures for specific situations. Prophylactic agents are administered before radiation exposure to prevent damage. 'Mitigation' designates agents (mitigators or mitigants) that are administered during or after radiation exposure with the aim of preventing or reducing the action of radiation on tissues before the onset of symptoms. Therapeutic agents are administered after radiation exposure to treat or facilitate recovery from various aspects of the acute radiation syndrome (ARS) and delayed effects of radiation exposure.

5.1 Radioprotectants

A radioprotectant is defined as any drug or agent that is used to block the adverse effects of exposure to ionizing radiation. Radioprotectants are used in a variety of settings including medical therapy- prevention of unwanted effects of therapeutic radiation, space travel, acute radiation syndrome or long-term health effects of unintentional exposure to high-dose radiation [9].

A wide variety of chemical and natural agents have been studied for their potential use as radioprotectants, although essentially are antioxidants or immunomodulators. Antioxidants can scavenge free radicals that are generated by the interaction of ionizing radiation with tissue water, thereby protecting macromolecules from radiation-induced damage. They are of limited utility in the setting of ARS, however, these compounds are most effective when administered prior to radiation exposure [9].

Exposure to ionizing radiation induces increased production of reactive oxygen species by the mitochondria. Thus antioxidants and free radical scavengers have long been studied for their potential in the treatment of radiation toxicity. Both synthetic compounds and natural products such as melatonin have been shown capable of attenuating DNA damage and improving cell survival, if present at the time of irradiation. However, their administration in the post-irradiation setting, i.e., following exposure to ionizing radiation, has not been as widely studied. Furthermore, toxicity occurs in spite of many antioxidants [10].

The polypeptide compound CBLB-502, which is derived from Salmonella flagellin, binds to toll-like receptor 5 (TLR5) and activates) signalling nuclear factor-kappaB (NF-kappaB. Studies in mice have confirmed its ability, when administered prior to lethal total-body irradiation, to protect against hematopoietic and gastrointestinal syndromes. Administered post-irradiation, the compound was also able to enhance survival in rodents, even at lower doses of radiation [11].

Immunomodulators can induce the release of cytokines, which stimulate the growth, differentiation and proliferation of hematopoietic stem and progenitor cells [9]. Candidate immunomodulators for treatment of ARS include the steroidal compound 5-androstenediol (Neumune), which has been shown preclinically to stimulate both innate and adaptive immune responses, treat infection and counter radioactivity-induced immuno-suppression. Granulocytes, lymphocytes and platelets are the most important cells to be regenerated, because these cells have a short half-life in circulating blood and are reduced rapidly after exposure to irradiation.

5.2 Radiomitigants

The principal drawback of radioprotectants in the treatment of acute radiation syndrome is their limited efficacy on postexposure.administration.Thus RxBio has reported a new "radiomitigant" approach exemplified by Rx-100, a small molecule that protects against damage to the bone marrow and critical cells of the small intestine. Rx-100 is essentially nontoxic at therapeutic doses and provides effective treatment of acute radiation sickness when administered up to 72 hours after exposure to lethal, whole-body radiation. The product boosts natural mechanisms that promote and sustain cell survival in almost every cell type, while also inhibiting the cascade leading to apoptosis. As a potent protector of the gastrointestinal tract, Rx-100 provides significant protection to the gut from radiation as well as other toxic substances. It maintains the mucosa of the gastrointestinal tract, and prevents severe diarrhea and the entry of bacterial toxins into the blood stream.

Researchers at the University of North Carolina have also studied the radiomitigant approach using the selective CDK4/6 inhibitor PD-0332991. Administered to mice prior to or up to several hours after total body irradiation, the enzyme inhibitor transiently arrests the cell cycle of hematopoeitic progenitor and stem cells in the bone marrow. This transient arrest, termed pharmacological quiescence, exploits that fact that cell cycle arrest makes cells resistant to DNA damage [12].

5.3 Cytokine Therapy

Acute exposure to ionizing radiation triggers apoptotic cell death of hematopoietic stem and progenitor cells

Table 2. Cell therapies in active development for the treatment of acute radiation syndrome

S.N.	Drug Name	Organi zation	Mechanism of Action	Status
1	Remestemcel-L	Osiris	Intravenous formulation of ex vivo cultured mesenchymal stem cells obtained from the bone marrow of volunteer donors aged 18–32 years	Clinical
2	CLT-008	Cellerant	Cell-based therapy that contains myeloid progenitor cells	Preclinical

Table 3. Drugs and biologics in active development for the treatment of acute radiation syndrome

S.N.	Drug Name	Organization	Mechanism of Action	Status
1	BIO-300	Humanetics	Antioxidants/ Tyrosine Kinase Inhibitors	Phase II
2	CBLB-502	Cleveland Biolabs	TLR5 Receptor Agonists	Phase II
3	Beclometasone dipropionate	Soligenix		Phase I/II
4	EA-230	Exponential Biotherapies		Phase I
5	ON-01210.Na	Onconova	Abl Kinase Inhibitors/ p38 MAPK Inhibitors/ Tyrosine Kinase Inhibitors/ p21-Activated Kinase (PAK) Inhibitors/ Apoptosis Regulators	Phase I
6	Sothrombomodulin-alfa	PAION	Inhibitors of Blood Coagulation Pathways/ Thrombin Inhibitors	Phase I
7	Remestemcel-L	Osiris		Clinical
8	BIO-100	Humanetics		Preclinical
9	BIO-200	Humanetics		Preclinical
10	BIO-400	Humanetics		Preclinical
11	BIO-500	Humanetics		Preclinical
12	CLT -008	Cellerant		Preclinical
13	EDL-2000	RxBio		Preclinical
14	Homspera	ImmuneRegen	Tachykinin NK1 A gonists/ Cytokine Production Promoters	Preclinical
15	MnDTEIP	Aeolus Pharm-aceuticals/EpiStem/ NIAID	Antioxidants/Superoxide Dismutase (SOD) Mimetics	Preclinical
16	RLIP-76	Terapio		Preclinical
17	RX-100	RxBio	Lysophospholipid edg2 (LPA1) Receptor Agonists/ Lysophosph Olipid edg4 (LPA2) Receptor Agonists/ Lysophospholipid edg7 (LPA3) Receptor Agonists	Preclinical
18	Rx-101	RxBio		Preclinical

(HSPCs), leaving the individual prone to infection and hemorrhage. Therefore the administration of antiapoptotic cytokines and colony-stimulating factors represents an important aspect of treatment of a patient with acute radiation syndrome.

A cocktail of cytokines may be administered, including stem cell factor, Flt-3 ligand, thrombopoietin and interleukin-3 (IL-3), with the objective of stimulating multilineage recovery [Singh, S et al 2008, Herodin, F et al 2005]; administration of granulocyte colony stimulating factor (filgrastim or pegfilgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) is used off-label to speed neutrophil recovery and stimulate residual hematopoiesis and is recommended in treatment guidelines [4, 5]. Scientific data supports the inclusion of tissue-specific cytokines such as keratinocyte growth factor and of pleiotropic agents such as erythropoietin or TNF -alpha in order to further increase the efficacy of cytokine combinations [7, 13].

5.4 Stem Cell Therapy

At higher radiation doses, cytokine therapy is ineffective because the population of residual HSPCs is insufficient to respond to cytokine supplementation. In the absence of contraindications (severe trauma,burns or gastrointestinal syndrome), patients with severe myeloablation due to ARS may thus be considered candidates for stem cell therapy, provided a suitable donor can be identified. Various stem cell sources have been proposed, including bone marrow, mobilized peripheral blood or cord blood [4, 13].

Transfusion of whole blood or peripheral blood mononuclear cells delivering myeloid progenitor cells has been proposed as a "bridging therapy" in patients who have suffered severe but not complete injury to the hematopoietic system. Transplanted progenitor cells might provide the necessary granulocytes, red blood cells and platelets during the critical period of bone marrow failure. Mobilization of progenitor cells from bone marrow into blood may be induced by G-CSF (filgrastim), plerixafor or tocopherol succinate. The feasibility of this procedure has been successfully demonstrated in murine models of ARS [14, 15].

CLT-008 is a cell-based therapy for the treatment of acute radiation syndrome that contains human myeloid progenitor cells derived from adult stem cells that mature into functional granulocytes, platelets and red blood cells in vivo. CLT-008 is intended to provide hematopoietic cellular support after exposure to ionizing radiation, and is being developed under the FDA's Animal Efficacy Rule (Table 2).

In 2007, Osiris and Genzyme announced the formation of a partnership to develop **Prochymal**, a highly purified formulation of mesenchymal stem cells grown in culture, for the treatment of acute radiation syndrome. This product is also being developed under the Animal Efficacy Rule, although it has been successfully tested in phase III studies for other indications. The long-term storage capability of Prochymal makes stockpiling the product feasible, for a mass-health event.

In addition to the specific mechanisms of action described above, other therapeutic drug classes have also been identified and evaluated for their potential in treating acute radiation syndrome, including apoptosis inhibitors and various herbal drugs and natural products [7, 9]. Table 3 presents an up-to-date overview of drugs and biologics in active preclinical and clinical investigation for the treatment of acute radiation syndrome, together with their indicated status of development.

6. Conclusion

The customary modalities used for the treatment of ARS relies on use of radioprotectors, radiomitigators and radiation therapeutics. Such radiation countermeasures will have potential in reducing accidental exposure occuring due to natural calamities like earthquakes and tsunami, as was seen in the case of Fukushima daiichi nuclear reactors., There is a need to locate more effective post-irradiation effective radioprotector that can accelerate the hematopoietic regeneration, to overcome such situations. Since the hematopoietic tissues are critical target for ionizing radiation, future, studies should focus on development of drugs that have potentiaityl to enhance the stimulation of hematopoietic stem cells used to replenish the radiation suppressed necessary immune cells.

7. Conflict of Interest

Authors declare that they do not have any conflict of interest.

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