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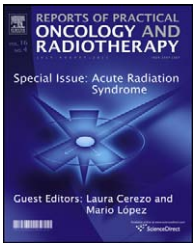

Review

Medical management of the acute radiation syndrome

Mario López, Margarita Martín*

Servicio Oncología Radioterápica, Hospital de la Princesa, Instituto de Investigación Princesa, Madrid, Spain

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ABSTRACT

The acute radiation syndrome (ARS) occurs after whole-body or significant partial-body irradiation (typically at a dose of >1 Gy). ARS can involve the hematopoietic, cutaneous, gastrointestinal and the neurovascular organ systems either individually or in combination. There is a correlation between the severity of clinical signs and symptoms of ARS and radiation dose. Radiation induced multi-organ failure (MOF) describes the progressive dysfunction of two or more organ systems over time. Radiation combined injury (RCI) is defined as radiation injury combined with blunt or penetrating trauma, burns, blast, or infection. The classic syndromes are: hematopoietic (doses >2–3 Gy), gastrointestinal (doses 5–12 Gy) and cerebrovascular syndrome (doses 10–20 Gy). There is no possibility to survive after doses >10–12 Gy.

The Phases of ARS are—prodromal: 0–2 days from exposure, latent: 2–20 days, and manifest illness: 21–60 days from exposure.

Granulocyte-colony stimulating factor (G-CSF) at a dose of 5 μg/kg body weight per day subcutaneously has been recommended as treatment of neutropenia, and antibiotics, antiviral and antifungal agents for prevention or treatment of infections.

If taken within the first hours of contamination, stable iodine in the form of nonradioactive potassium iodide (KI) saturates iodine binding sites within the thyroid and inhibits incorporation of radioiodines into the gland.

Finally, if severe aplasia persists under cytokines for more than 14 days, the possibility of a hematopoietic stem cell (HSC) transplantation should be evaluated.

This review will focus on the clinical aspects of the ARS, using the European triage system (METREPOL) to evaluate the severity of radiation injury, and scoring groups of patients for the general and specific management of the syndrome.

1. Introduction

The acute radiation syndrome (ARS) is a broad term used to describe a range of signs and symptoms that reflect severe damage to specific organ systems and that can lead to death within hours or up to several months after exposure.[1] The ARS occurs after whole-body or significant partial-body irradiation of greater than 1 Gy, over a short time period (high dose rate).

* *Corresponding author at*: Servicio Oncología Radioterápica, Hospital de la Princesa, C/Diego de León 62, CP 2006 Madrid, Spain. Tel.: +34 91 5202332; fax: +34 91 5202315.
E-mail address: mlopezrgez@yahoo.es (M. López).

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Radiation injury can occur from external irradiation; external contamination with radioactive materials; and internal contamination by inhalation, ingestion, or transdermal absorption with incorporation of radiologic materials into cells and tissues. The reaction of an individual to an exposure depends on a number of independent variables, including the dose, the dose rate, the nature and energy of the radiation, the type and volume of tissue irradiated, age and state of health, and the quality of medical care available.[2]

Three forms of energy are released from a nuclear detonation: heat, accounting for approximately 35% of total energy; shock or bomb blast, accounting for approximately 50% of total energy; radiation, accounting for the remaining 15% of total energy.

Our aim is to review the clinical aspects of the ARS, how to assess the severity of radiation injury, and evaluate the different treatments for the syndrome.

2. Biology and clinical features of radiation injury

Several factors determine the lethality of ionizing radiation. These include:

(a) *Dose rate*: Doses received over a shorter period of time cause more damage.
(b) *Distance from the source*: For point sources of radiation, the dose rate decreases as the square of the distance from the source (inverse square law).
(c) *Shielding*: Can reduce exposure, depending upon the type of radiation and the material used.[3]
(d) *Available medical therapy*: Is critical for those exposed to moderately high doses of radiation.

The lethal dose at 60 days (The LD50/60 is defined as the dose necessary to cause death in 50% of an irradiated population in 60 days) for humans has been estimated to be approximately 3.5–4.0 Gy in persons managed without supportive care, 4.5–7 Gy when antibiotics and treatment support are provided, and potentially as high as 7–9 Gy in patients with rapid access to intensive care units, reverse isolation, and hematopoietic cell transplantation.[4,5] There is virtually no chance of survival following a total body exposure in excess of 10–12 Gy.

Ionizing radiation may interact directly with intracellular targets or may interact with other molecules (e.g., water) to produce free radicals that, in turn, reach and damage a target (e.g., DNA, mRNA, proteins, plasma membrane). The most critically affected tissues in adults include the following: spermatocytes in the testis, hematopoietic precursor cells in the bone marrow and crypt cells in the intestines.

Dose-dependent effects on various organs have also been identified. They are of two types, deterministic and stochastic:

(a) A deterministic effect is one in which the severity is determined by the dose (e.g., depression of blood counts). A dose threshold is characteristic of this effect. As an example, the threshold absorbed dose for a "deterministic effect" on bone marrow (0.5 Gy) is lower than that for all other organs, except for the testis (0.15 Gy).
(b) A stochastic effect represents an outcome for which the probability of occurrence (rather than severity) is determined by the dose. An example is radiation-induced carcinogenesis, which occurs after a prolonged and variable delay (latency) after exposure. These effects do not have an apparent threshold dose.

3. Assessment of radiation dose

(a) *Physical measurement*: Physical dosimetry can provide an estimate of individual dose, using a whole-body radiation dosimeter. Few whole-body dosimeters are available for rapid assessment of dose. Reconstruction of dose can be made with considerable sensitivity, using environmental measurements combined with time-integrated activity.[6,7] However, this is a time-consuming process that is impractical in an emergency situation, particularly when there are many potentially exposed persons.
Estimation of the internal dose from the deposition of radioactive materials, such as alpha emitters (e.g., plutonium, americium, californium) and beta-gamma emitters (e.g., cesium, cobalt and iodine) into the lungs, gastrointestinal tract, and other tissues, requires detection with special instrumentation (such as ion chambers and spectroscopes). In this case, measurements are made on body fluids (blood, urine and saliva), nasal swipes, fecal samples, and/or expired air.[8]
(b) *Biological and clinical markers*: Currently, the three most clinically useful markers are the time to onset of emesis, lymphocyte depletion kinetics, and chromosomal aberrations. Monitoring the decrease in absolute lymphocyte count has been found to be the most practical method to assess the radiation dose within hours or days following a radiation exposure.[9] The time to emesis and lymphocyte depletion kinetics are dose-related and are amenable to quantitative analysis with respect to dose.[10] The rate of decline and nadir of the absolute lymphocyte count over the initial 12 h to 7 days after exposure is a function of cumulative dose. Lymphocyte depletion kinetics predict dose for a photon-equivalent dose range between 1 and 10 Gy with an exposure resolution of approximately 2 Gy.[2,9] The three elements (i.e., time to onset of vomiting, lymphocyte depletion kinetics, and chromosome aberrations) should be sought for the most accurate assignment of prognosis and selection of therapy. As a practical matter, however, only the time of onset of vomiting and lymphocyte depletion may be available within the first 24 h following exposure.
(c) *Chromosomal changes*: The frequency of chromosomal aberrations (e.g., dicentrics, chromosomal rings) in lymphocytes are correlated to radiation dose.[11] A peripheral blood sample should be obtained at 24 h after exposure (or later) in accordance with the policies of a qualified radiation cytogenetic biodosimetry laboratory. Because of incubation times, results will not be available for 48–72 h after the sample has been submitted for analysis.[12]

Initial laboratory testings according to European consensus, within the first 48 h are[13]:

(a) Repeated blood cell counts (lymphocites, granulocytes and platelets) if possible every 4–8 h for the first 24 h, then every 12–24 h (+reticulocytes).
(b) Chromosome aberration analysis on blood lymphocytes (biodosimetry).
(c) Red cell group typing.
(d) Store serum and cells for DNA for future analyses including HLA typing upon request from clinical teams.
(e) Standard biochemical tests (+amylasemia).
(f) If there is suspicion of a neutron exposure, a blood sample of 20 ml should be taken to measure the content of radioactive sodium (^{24}Na).
(g) Urine and feces if radionuclide contamination is suspected.

The time of CBC collection must be carefully noted, because of important time-related changes in the lymphocyte count. Additional monitoring should be based on the whole-body dose, as the onset of neutropenia and its severity are dose dependent. Patients with low exposures may need a weekly or twice-weekly CBC for 4–6 weeks to document their WBC nadir and subsequent recovery.

The various cytogenetics methods, including dicentric assay (DA) and fluorescence in situ hybridization (FISH) assay, offer high-accuracy exposure dose determination, yet require a long sample-processing time.

4. Scoring the severity of radiation exposure

The European protocol METREPOL (Medical Treatment Protocols for radiation accident victims; this protocol forms the basis of a computarized guidance system) agreed that the first 48 h after a radiological accident involving masses of people are crucial. In that time period, the accident victims should be processed by an emergency triage system where the patients are scored on the basis of both clinical and biological criteria, including the delay before symptoms appear, the delay before cutaneous erythema is observed, the severity of asthenia, the intensity of nausea, the frequency of vomiting per 24 h, the severity and frequency of diarrhea or number of stools per 24 h, the presence of abdominal pain, the intensity of headaches, temperature, blood pressure, and the occurrence of temporary loss of consciusness[13,14] (Table 1).

Patients with a score of 1 can be followed up on an outpatient basis or be treated by the equivalent of a day care hospital. Patients with a score of 2 are those patients who need maximum medical attention if they are to survive. Patients with a score of 3 are those patients who are predicted to develop multi-organ failure (MOF) and unfortunately have almost no hope of recovering. Radiation induced multi-organ failure (MOF) describes the progressive dysfunction of two or more organ systems over time.

A primary objective in the first 48 h is to identify bystanders who were not irradiated (score 0). This will help to prevent hospitals from exceeding their saturation capacity. The patients who are hospitalized are only those who have a score exceeding 1. In the case of accidental contamination, only those patients who have been appropriately decontaminated should be admitted.

After the initial 48 h, scoring of the patient is re-evaluated on the basis of METREPOL.[15] Patients who receive a score of 2 or 3 then receive the recommended treatment, regardless of whether they have any hope of recovering. It is unfortunately not possible to know during the first 48 h the individual physical and biological dosimetry: these key pieces of information only become accessible after 48 h, at which point they become the basis of further medical decision-making. It should be noted that which body portion of an individual is exposed is more important than the overall dose of exposure.

Some authors propose screening methods based on high-accuracy biodosimetry such as in vivo electron paramagnetic resonance (EPR) dosimetry of tooth and nail tissue for triage during a catastrophic nuclear event.[16]

5. Contamination

Once the patient is medically stabilized, alpha and Geiger counters must be used to evaluate radioactivity and documented on an anatomic chart. To assess the possibility of internal contamination, separate saline or water moistened swabs should be used to wipe the skin, nares, ears, mouth, and wounds. These swabs should be assessed for radioactivity with a Geiger counter or alpha-radiation detection device.[17]

Decontamination should begin with debridement of open wounds to remove as much debris as possible. Wounds should be copiously irrigated with normal saline until they are free of radioactivity, and then covered with a waterproof dressing. Contaminated burns should be treated as any other thermal or chemical burn.[18]

Patients with internal contamination usually pose no hazard to caregivers or to the medical facility, although their fecal and urinary excretion products should be measured for radioactivity and disposed of in marked, sealed containers.[19]

Chelating agents such as dyethilene-triamine-pentacetic acid (DTPA) as the zinc or calcium salts (Zn and Ca-DTPA) can expedite the removal of radioisotopes such as plutonium-239 or yttrium-90. Sodium bicarbonate is used to treat renal chemical toxicity of uranium and reduce the risk of acute tubular necrosis (which is generally a far greater hazard than its radiologic toxicity). Oral administration of insoluble Prusian blue is the countermeasure of choice for Cesium-137 (found in high concentrations for miles around Chernobyl following the accident) rubidium-82, or thallium-201. Oral calcium or aluminium phosphate solutions can block the absorption of strontium through competitive inhibition.

Radioiodines are known from Chernobyl data to cause thyroid injury and to be carcinogenic, especially to the fetus and to children under 18 years of age. If taken within 4–6 h of contamination, stable iodine in the form of nonradioactive potassium iodide (KI) saturates iodine binding sites within the thyroid and inhibits incorporation of radioiodines into the gland[20]; ^{131}I and ^{137}Cs are the most significant for dose received by the exposed population in Chernobyl.

Table 1 – Primary scoring (first 48 h).

	Score 1	Score 2	Score 3
Average delay before symptoms appear	Less than 12 h	Less than 5 h	Less than 30 min
Cutaneous erythema	0	+/–	+++; before 3 h
Asthenia	+	++	+++
Nausea	+	+++	++++
Vomiting per 24 h	Maximum 1	1–10	Above 10; intractable
Diarrhea/number of stools per 24 h	Maximum 2–3; bulky	2–9; soft	Above 10; watery
Abdominal pain	Minimal	Intense	Excruciating
Headache	0	++	Excruciating; signs of cranial HT
Temperature	Below 38 °C	38–40 °C	Above 40 °C
Blood pressure	Normal	Normal; possible temporary decrease	Systolic below 80
Temporary loss of consciousness	0	0	+/coma
Depletion of blood lymphocytes			
At 24 h	Above 1500/mcl	Below 1500/mcl	Below 500/mcl
At 48 h	Above 1500/mcl	Below 1500/mcl	Below 100/mcl
	Outpatient monitoring	Hospitalization for curative treatment	Hospitalization multi-organ failure (MOF) predicted

6. Phases of acute radiation injury

The most rapidly dividing cells are the most sensitive to the acute effects of radiation. Symptoms arising from such exposures are referred to as acute radiation syndrome (ARS).

Classically, the threshold dose for ARS is a whole-body or significant partial-body irradiation of greater than 1 Gy delivered at a relatively high dose rate. The signs and symptoms of ARS are related to the whole-body absorbed dose of radiation. Doses less than 0.5 Gy are not expected to cause acute symptoms, whereas doses of 4.5 Gy are lethal to 50% of exposed persons. The ARS progresses through three phases[21]:

a) *Prodromal phase*: 0–2 days after exposure.
b) *Latent phase*: 2–20 days after exposure.
c) *Manifest illness*: 21–60 days after exposure.

The onset, duration, and dominant manifestation of the syndrome depend upon the dosage of radiation received. Acute changes, which are seen within the first 2 months following exposure, include signs and symptoms resulting mainly from damage to the skin, CNS, lung, GI tract, and hematopoietic tissues. Classic clinical syndromes associated with ARS include the hematopoietic, gastrointestinal, and cerebrovascular syndromes, although there is significant overlap[22] (Table 2). The cutaneous syndrome (CS) is especially common and important in patients with ARS consequent to a non-uniform exposure. The CS may include changes ranging from epilation to radionecrosis.

6.1. *Prodromal phase*

Early symptoms resulting from an acute total-body exposure constitute the prodromal radiation syndrome. These early symptoms include anorexia, apathy, nausea, vomiting, diarrhea, fever, tachycardia and headache and are dependent on the magnitude of radiation dose and the presence of additional injury. The prodromal syndrome is generally mild or absent at total body doses of 1 Gy or less. Onset of symptoms within the firs 2 h usually indicates significant and potentially lethal exposures exceeding 2 Gy. At these doses, the gastrointestinal syndrome adds to the symptomatology. At high doses (e.g., 10 to >20 Gy), prodromal symptoms occur in virtually all patient within minutes of exposure.[23,24] The cerebrovascular syndrome appears and death often occurs within few days to weeks after such exposures. Those patients who do not present with the cerebrovascular syndrome but develop the gastrointestinal syndrome may survive with appropriate medical support. However, all will also develop the hematologic syndrome if they survive long enough. The cutaneous syndrome may develop in any of the above scenarios and will complicate management.

6.2. *Cerebrovascular syndrome*

In general, cerebrovascular symptoms only occur at whole-body doses in excess of 10 Gy. Also called neurovascular syndrome or CNS syndrome, results from localized changes in the central nervous system. These include impaired capillary circulation with damage to the blood–brain barrier, interstitial edema, acute inflammation, petequial hemorraghes, inflammation of the meninges, and hypertrophy of perivascular astrocytes.[15] Presence of swelling and edema may be documented by CT scans and MRI of the head. With doses in the range of 10–20 Gy, individuals present with persistent and severe nausea and vomiting, accompanied by headache, neurologic deficits, and abnormal cognition. Signs and symptoms include disorientation, confusion, loss of balance, and seizures. Physical examination may show papilledema, ataxia, and reduced of absent deep tendon and corneal reflexes.

Table 2 – Radiation effects.

Dose (Gy)	20 and above	Neurovascular syndrome onset	(>10 Gy) Multiple organ failure probable death (8–10 Gy) Consider stem cell transplant
	6 Gy	GI syndrome onset	(6–7 Gy) LD50/60 with supportive care (3–5 Gy) LD50/60 without treatment
	1 Gy	Hematopoietic syndrome onset	(0–2 Gy) ~100% survival without treatment

6.3. *Gastrointestinal syndrome*

The gastrointestinal syndrome typically develops within five days of the initial exposure. At doses < 1.5 Gy, only the prodromal phase of nausea, vomiting, and gastric atony are observed.[25] More severe symptoms develop at doses between 5 and 12 Gy,[26] secondary to loss of intestinal crypt cells and breakdown of the mucosal barrier. These changes result in crampy abdominal pain, diarrhea, nausea and vomiting, gastrointestinal bleeding with resultant anemia, and abnormalities of fluid and electrolyte balance. This early phase is often followed by a latent phase lasting 5–7 days, during which symptoms abate. Vomiting and severe diarrhea accompanied by high fever make up the manifest illness. Systemic effects at this time may include malnutrition from malabsorption. Impaired barrier function of the gastrointestinal tract results in the passage of bacteria and their toxins through the intestinal wall into the bloodstream, predisposing to infection and sepsis, which may further be compromised by immunosuppression and cytopenia secondary to development of the hematopoietic syndrome. Other severe complications include ulceration and necrosis of the bowel wall, leading to stenosis, ileus, and perforation.

6.4. *Hematopoietic syndrome*

The hematopoietic syndrome resulting from radiation injury occurs at whole-body doses of 2–3 Gy or higher.[27] In addition to inducing apoptosis, whose effect is not seen before the first cell cycle following radiation exposure, radiation alters recirculation properties of lymphocytes.[28] Neutropenia and thrombocytopenia reach a nadir at 2–4 weeks and may persist for months. Anemia inevitably ensues, due to the combined effects of gastrointestinal blood loss from the gastrointestinal syndrome, hemorraghe into organs and tissues secondary to thrombocytopenia, and, ultimately, bone marrow aplasia.

In the ensuing weeks to months after exposure, hypoplasia or aplasia of the bone marrow occurs, resulting in pancytopenia, predisposition to infection, bleeding, and or poor wound healing, all of which may contribute to death in the absence of appropriate supportive care. Inhomogeneity of dose, afforded by partial shielding or a more ventral exposure may imply bone marrow sparing. Such sparings contribute to the reestablishment of hematopoiesis.

Selective radioresistant subpopulations of stem cells and/or accessory cells exist. Subpopulations of stem cells or accessory cells are selectively more radioresistant, presumably because of their largely noncycling (Go) state.[29,30] These may play an important role in recovery of hematopoiesis after exposure to doses as high as 6 Gy, albeit with a reduced capacity for self-renewal.[31]

Lymphopenia is common and occurs before depression of the other cellular elements, and may develop within the first 6–24 h after exposure to a moderate to high dose.[9] A 50% decline in the absolute lymphocyte count within the first 24 h after exposure, followed by a further more severe decline within 48 h, characterizes a potentially fatal exposure in the range of 5–10 Gy. An absolute lymphocyte count that remains within 50% of normal during the first week following exposure suggests an exposure of <1 Gy and a survival probability in excess of 90%. However, since lymphopenia can also result from stresses accompanying burns and trauma,[32,33] it is always important to examine more than one biodosimetry element (e.g., prodromal symptoms, lymphocyte dicentrics) whenever possible.

The initial neutrophil nadir occurs at approximately 1 week following exposure, after which there may be an abortive, transient rise in the absolute neutrophil count following exposure to doses less than 5 Gy. Presence of this abortive rise may indicate a survivable exposure.[34] A more profound and longer-lasting neutrophil nadir occurs at 2–4 weeks post-exposure, and may last for many weeks.

6.5. *Cutaneous syndrome*

The cutaneous syndrome may develop early following exposure (e.g., 1–2 days). However, it may take years before becoming fully manifest. Early lesions include erythema, edema, and dry descamation of the skin. More advanced lesions include bullae, moist descamation, ulceration, and onycholisis.[35,36] Ulceration may be limited to the epidermis or may involve deeper structures, such as dermis, subcutaneous tissue, and even muscle and/or bone.

7. Treatment of radiation injury

Patients with acute, high dose, whole body irradiation will fall into one of three categories: those who recover with minimal intervention; those who require aggressive supportive care, up to and including bone marrow stem cell transplants; those who, due to the dose they received, concomitant physical trauma, or inadequate clinical resources, will be triaged to receive palliative care. Treatment of the ARS is not indicated when exposure dose is very low (<1 Gy) or very high (>10 Gy).

Obtaining a history and physical examination, removal of external contamination, dose estimation, supportive care (including psychological support of the patient and family), symptomatic treatment, and replacement of fluids and electrolytes should be the earliest goals of medical management.[37] Reverse isolation is needed for patients with whole body doses greater than 2–3 Gy and antacids and H2 blockers should be avoided to maintain gastric acidity, using sucralfate to prevent stress ulcers.[22]

Beyond the first 48 h, a second patient scoring is done by organs (neurovascular, hematopoiesis, cutaneous and

Table 3 – Initial therapeutic management.

Score 1: Monitoring no cytokine
Outpatient clinical monitoring.
Blood count: every day for 6 days, then once a week for 2 months.
Score 2: Cytokines (curative)
G-CSF/KGF should be used as early as possible for 14–21 days.
EPO and stem cell factor questionable.
Symptomatic treatment for gastrointestinal damage.
If severe aplasia: protected environment.
Accidental radiation exposure is generally heterogeneous; some under-exposed/protected regions of bone marrow can give rise to endogenous hematopoietic recovery.
Score 3: Cytokines (until reappraisal of score)
Palliative/symptomatic treatment.
Re-evaluation during the first week based on laboratory or clinical.
Symptoms revealing irreversible organ damage/disfunction.

gut) according to the METREPOL Document for therapeutic management and multiple organ failure (MOF) prediction[14] (Table 3).

Surgical intervention, when required, should be carried out within 36 h, and not later than 48 h after exposure.[38] Additional surgery, if required, should not be performed until at least 6 weeks post-exposure, in order to assure recovery from the period of cytopenia and immunosuppression, which would otherwise seriously add to the risk of developing surgical complications (i.e., infection and poor wound healing).

Following a large release of radioactive iodine, which is unlikely with a radiologic dispersal device but probable with a nuclear weapon or power plant incident, public health officials may recommend administration of potassium iodide (KI), especially to children and pregnant women (Table 4).[39]

The following dosages of selective 5-HT3 receptor antagonists are recommended for radiation-induced emesis[22]:

Ondansetron—Initial: 0.15 mg/kg IV; a continuous IV dose option consists of 8 mg followed by 1 mg/h for the next 24 h. Oral dose: 8 mg/8 h as needed.

Granisetron—Oral dosage form (tablets): Dose is usually 1 milligram (mg) initially and repeated in 12 h after the first dose. Alternatively, 2 mg may be taken as one dose. IV dose is based on body weight; it is typically 10 μg (mcg) per kilogram (kg) of body weight.

Table 4 – Potassium iodide recommended doses.

Adults >40 years of age with thyroid exposure ≥5 Gy	130 mg day^{-1}
Adults 18–40 years of age with thyroid exposure ≥0.1 Gy	130 mg day^{-1}
Pregnant or lactating women with thyroid exposure ≥0.05 Gy	130 mg day^{-1}
Children and adolescents 3–18 years of age with thyroid exposure ≥0.05 Gy	65 mg day^{-1}
Infants 1 month to 3 years of age with thyroid exposure ≥0.05 Gy	32 mg day^{-1}
Neonates from birth to 1 month with thyroid exposure ≥0.05 Gy	16 mg day^{-1}

7.1. *Blood products*

Severe degrees of anemia and thrombocytopenia do not typically occur before 2–4 weeks following exposure, during which time a sufficient number of additional blood donors may be identified when there are large numbers of injured patients.

Unless the victim is known to have received <1 Gy irradiation, all cellular products should be irradiated (25 Gy) to prevent transfusion-associated graft-versus-host disease, and leukoreduced (except granulocyte transfusions) to diminish the risk of febrile non-hemolytic reactions, immunosuppressive effects of blood transfusions, platelet alloimmunization and cytomegalovirus infection.[40] Transfusion of platelets remains primary therapy to maintain adequate platelet counts. Requirement for platelet support depends on patient's condition. In irradiated patients with or without other major medical problems, platelets should be maintained at greater than 20 000/(L. If surgery is needed, platelet count should be greater than 75 000/(L.

Use of erythropoietin (Epo) anemia therapy after radiation injury is not recommended even though probably safe as anemia is not generally life-threatening in this situation.[41] There is general agreement that granulocyte colony-stimulating factor (G-CSF) is an acceptable choice for treatment of individuals receiving a whole-body dose of 3 Gy or more, or when clinical signs and symptoms indicate a level 3 degree of toxicity.

Individuals receiving a whole-body dose of 2 Gy with mechanical trauma and/or burns (i.e., combined injury) are candidates for cytokine therapy, as are individuals at extremes of age (i.e., children < 12 years of age and the elderly). Since studies in animals suggest that the risk for developing the hematopoietic syndrome may be reduced when cytokines are administered early after exposure (i.e., in the first 24 h when apoptosis occurs), it has been recommended that CSFs be initiated as soon as possible after receipt of a survivable whole-body dose of radiation. Granulocyte-colony stimulating factor (G-CSF) at a dose of 5 μg/kg body weight per day subcutaneously has been recommended as treatment in this setting. Other cytokines (e.g., pegylated G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF) or KGF (keratinocite grow factor) may be considered. Cytokine therapy should be continued for 2–3 weeks or until the absolute neutrophil count is >1000/μL. On the other hand, individuals with degree four hematopoietic toxicity are unlikely to have responsive hematopoietic stem-progenitor cells. These individuals are candidates for stem-cell transplantation. In this case, cytokines may be useful in conjunction with the infusion of hematopoietic stem/progenitor cells. The following cytokines are available for patients expected to experience severe neutropenia[27]:

Filgrastim (G-CSF) 2.5–5 μg/kg/d subcutaneously or the equivalent (100–200 μg/(m^2 d)).
Sargramostim (GM-CSF) 5–10 μg/kg/d subcutaneously or (200–400 μg/(m^2 d)).
Pegfilgrastim (pegG-CSF) 6 mg once subcutaneously.

7.2. *Antibiotics*

Susceptibility to local and systemic infection after radiation arises as a result of breeches in cutaneous and mucosal barriers or immune suppression and neutropenia prophylaxis should include a fluoroquinolone (e.g., levofloxacin), an antiviral agent (acyclovir or one of its congeners), and an antifungal agent (fluconazol). For those who experience fever and significant neutropenia (i.e., absolute neutrophil count < 500/μL), broad spectrum prophylactic antimicrobials should be employed, as the neutropenic duration is likely to be prolonged. The first approach is intravenous (IV) antibiotic monotherapy with either imipenem/cilastatin, meropenem, piperacilin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime). The second approach is IV antibiotic combination therapy: aminoglycoside or cyprofloxacine plus antipseudomonal penicillin or aminoglycoside plus antipseudomonal cephalosporine. The third approach is the addition of IV Vancomycin for specific indications either to IV monotherapy or to combination therapy.[42] These agents should be continued until the patient fails treatment, experiences a neutropenic fever, or experiences neutrophil recovery (ANC > 500/μL).

The incidence of reactivation of cytomegalovirus (CMV) in those patients harbouring a latent CMV infection may be increased. If resources permit, CMV serologic status should be assessed. Patients with evidence of early viremia should be treated pre-emptively, prior to the development of CMV disease, with either ganciclovir or valganciclovir. For those patients with a history of CMV reactivation and continued T-cell immunodeficiency (i.e., CD4 count < 50/μL), more protracted monitoring should be considered, such as every other week until 6 months post-exposure.

The opportunistic pathogen pneumocystis jirovecii (p. carinii) has unique tropism for the lungs, with rare dissemination. Patients with profound T-helper cell depletion (i.e., absolute CD4 count < 200/μL) are at risk for infection. Prophylaxis is warranted, given its associated high mortality, although no defined guidelines for monitoring of the CD4 count in irradiation patients exist. Extrapolating from the HIV and stem cell transplant experience, the absolute CD4 count should be assessed at approximately day 30 post-exposure, and the every 3–6 months until the absolute CD4 count is >200/μL. Initiation and maintenance of prophylaxis is recommended if the absolute CD4 count is <200/μL. In patients with persistent myelosupression, trimethoprim-sulfamethoxazole should be avoided as it may worsen existing cytopenias.[43] Discontinuation of prophylaxis can be considered when the CD4 count is >200/μL (Table 5).

7.3. *Hematopoietic cell transplantation*

In the course of treatment of a patient suffering from ARS, it may become necessary to perform a detailed analysis of the residual hematopoiesis in an effort to predict from hematopoietic recovery. A bone marrow aspirate, possibly complemented by a bone marrow biopsy, avoiding the evident sites of radiation exposure, may be useful during days 14–21.

The METREPOL conference experts agreed that hematopoietic stem cell (HSC) transplantation should not be performed on radiation accident victims who have the potential of endogenous hematopoietic recovery. Thus, emergency HSC transplantation is not a necessity in accidental whole body irradiation. Although a sample for HLA typing should be taken immediately and the search for potential donor initiated early, the transplant itself should not be carried out before a minimum observational period of 14–21 days has elapsed[13,14] (Table 6). The use of hematopoietic cell transplantation (HCT) in these patients is complicated by a variety of factors:

(a) Radiation exposure is often not homogeneous. Some parts of marrow-containing structures might be minimally or uniradiated because the patient was partially shielded by a barrier.
(b) Concomitant injuries such as burns or trauma can greatly complicate the care of patients who also have radiation-induced bone marrow failure.
(c) Explosion of a nuclear device leading to mass casualties would also destroy the infrastructure necessary to care for these patients.

Table 5 – Specific therapeutic management.

No treatment if dose <1 Gy or >10 Gy.
Decontamination and use of chelating agents: DTPA, Prusian blue and calcium/aluminium phosphate.
Potassium iodide (KI): saturates iodine binding sites within the thyroid and inhibits incorporation of radioiodines into the gland.
Surgery when necessary must be realized during the first 36 h.
Platelet transfusion if <20000/mcl (>75000/mcl if surgery needed).
Prophylaxis of neutropenia: fluoroquinolone + antiviral + antifungal.
Neutropenia and fever: broad spectrum prophylactic antimicrobials.
Serologic Citomegalovirus (CMV) status.
Pneumocystis Carinii prophylaxis if CD4 < 200/μL.

Table 6 – Hematopoietic stem cell (HSC) transplantation.

HSC transplantation is not an emergency
It is crucial to avoid GVDH in order not to compromise an endogenous recovery.
If severe aplasia persists under cytokines for more than 14 days, possibility of an hematopoietic stem cell (HSC) transplantation.
Criteria to transplant:
Severe marrow aplasia persisting 14–21 days
No residual hematopoiesis
No irreversible organ damage
Type of graft:
Bone marrow
Peripheral blood HSC
Cord blood
Donnor in the following order of priority:
Identical twin
Family member matched for a minimum of 7/8 HLA antigens
Unrelated donor matched for 9/10 antigens
Cord blood matched for at least 4/6 antigens
Source of stem cells (minimum doses of infusion):
2×10^6 CD34/kg (peripheral blood)
2×10^8 nucleated cells/kg (bone marrow)
3×10^7 nucleated cells (cord blood))

Only a fraction of patients might benefit from HCT (i.e., doses of 7–10 Gy for those receiving allogenic HCT and 4–10 Gy for those able to receive autologous or syngenic HCT).

8. Late effects

Leukemia was the first malignancy to be linked to radiation exposure among atomic bomb survivors and has the highest radiation-related relative risk of all cancers, particularly after exposure in childhood. Increased risk has been observed in numerous epidemiological studies, with risks becoming apparent relatively soon after exposure (2–5 years).[44]

The most significant scientific lesson learned from Chernobyl accident is that exposure to internal radiation in childhood and adolescence causes an increase in papillary thyroid cancer. Twenty-five years after the accident, thyroid cancer risk in exposed young people continues to be significantly elevated. Although the main health effect of radiation from the Chernobyl accident observed to date is the dramatic increase in thyroid cancer among persons exposed at young ages, increases in the incidence of other types of cancer, in particular breast cancer, have also been reported, but have not been conclusively linked to radiation from the accident.[45]

Recently, evidence has also emerged suggesting that moderate doses of ionizing radiation can contribute to excess cardiovascular disease risks.[46]

Radiation injury to the lung is an important, medically difficult aspect of high-dose radiation incidents. These complications may arise due to doses to the lungs in excess of 8–10 Gy. Radiation-associated tissue hypoxia often perpetuates further lung injury. Depending on the dose/dose rate and volume of lung irradiated, acute radiation pneumonitis may develop, characterized by dry cough and dyspnea. Fibrosis of the lung, which causes further dyspnea, is a possible late complication.[22]

During the first trimester period of organogenesis, the embryo is sensitive to growth-retarding effects because of the criticality of cellular activities and the high proportion of radiosensitive cells. For uterine doses > 0.5 Gy, growth retardation, gross congenital malformations, and microcephaly have been the predominant effects. The highest risk of mental retardation is irradiation of the fetus during the period of major neuronal migration (8–15 weeks) and the incidence is dose dependent. At 1 Gy fetal dose, approximately 75% will experience mental retardation. Conversely, at 16–25 weeks gestation, the fetus shows no increase in mental retardation at fetal doses < 0.5 Gy.[22]

9. Conclusion

Radiation oncologists, nuclear medicine specialists, hematologists, and health physicists, because of their knowledge of radiation and its biologic effects, will have to contact other physicians, staff and authorities, for training and evaluating local infrastructures for the management of the acute radiation syndrome.

Health personnel must be prepared for a major radiologic incident associated with the detonation of nuclear weapon or improvised nuclear device, the meltdown of a nuclear reactor, or the dispersal of radioactive contamination, such as by a radiologic dispersal device.

Further studies of cancer risk with analyses of gene-radiation interactions, are also of particular importance to understand the radiation mechanisms and improve radiation protection practice both in the case of further accidents and for the protection of patients with medical exposures.

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