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IN-DEPTH REVIEW

Medical management of radiation injuries: current approaches

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Abstract The current approach to medical management of irradiated patients begins with early diagnosis of radiation injury. Medical assessment of radiation dose is based on event history, symptomatology and laboratory results, with emphasis on time to emesis and lymphocyte depletion kinetics. Dose assessment provides a basis for early use of haematopoietic growth factors that can shorten the period of neutropaenia for patients with acute radiation syndrome. Assessments of haematopoietic, gastrointestinal and cutaneous syndromes have improved in recent years, but treatment options remain limited. Selected examples of current developments are presented.

Key words Combined injury; gastrointestinal syndrome; haematopoietic syndrome; internal contamination; local radiation injury; radiation injury; radiation medicine.

Introduction

New technologies and research during the past 20 years have provided a greater understanding of the complex nature of radiation injury at molecular, cellular, tissue and organ system levels. The experience gained both in radiation therapy and in medical care of radiation accident patients has enabled development and use of new assessment and treatment modalities and provided more information about complications and numerous problems yet to be solved. Little can be done currently to prevent reproductive and apoptotic death of cells after radiation injury, but current therapy has potential to facilitate production of certain cells, provide replacement therapy for lost haematopoietic cells, minimize infectious complications, minimize fibrosis formation and improve supportive care.

Although radiation accidents are not common, human error, failure to follow safety precautions and inadequate control/regulation of radiation sources have led to deaths and significant exposures among workers and members of the public. Table 1 summarizes 60 years of human experience.

Physicians practising occupational medicine may be involved in immediate assessment and care of radiation accident victims. Under ordinary circumstances, they would not be involved in the treatment phase of the acute radiation syndrome (ARS) or serious local injuries, although they might be called on to explain procedures or prognoses to patients and their families. Their knowledge of triage, assessment, initial diagnostic methods and general treatment protocols, however, would be of great value in any radiation accident or incident involving harm to individuals. This paper will review some current approaches to triage, assessment, therapy and supportive care of irradiated victims. The psychological aspects of radiation accidents, although very important, are beyond the scope of this paper.

Initial assessment and diagnosis

Four factors are critical determinants in the initial medical management of victims presenting at a hospital or clinic following an accidental or malevolent act involving radiological or nuclear materials:

(i) The number of victims involved. The ability to assess, diagnose and provide initial therapy may be compromised when large numbers of patients arrive for treatment. Triage is essential when personnel and material resources are scarce.

(ii) The presence/absence of thermal or conventional injuries. In incidents involving thermal or conventional injuries, along with total body or large volume partial body irradiation (i.e. combined injury), initial triage, assessment and treatment must first focus on the conventional injuries present. Diagnosis of the ARS and estimates of severity are made after the immediate lifesaving treatment of trauma, since the radiation injury does not present immediate life-threatening complications.

(iii) The amount of time that has elapsed since the exposure(s) occurred is important since victims presenting soon after being irradiated (i.e. minutes to 48 h) will have signs and symptoms and laboratory results that are different from those found in patients presenting days or

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Table 1. Major radiation accidents: human experience 1944–March, 2005

	No. of accidents	No. of persons involved	Significant exposures*	Fatalities
Total REAC/TS Registry (DOE, NRC dose criteria)*	US 252	1347	799	30
	Non-US 176	132 457	2251	104
	Total 428	133 804	3050	134
Former Soviet Union (FSU) data Registry (incomplete data)	137	507	278	35
Total REAC/TS and FSU data	565	134 311	3328	169

DOE, Department of Energy; NRC, Nuclear Regulatory Commission.

Source: REAC/TS, Oak Ridge Institute for Science and Education, Oak Ridge, TN, USA.

weeks after exposures. Late presenting patients are likely to be sicker, with problems such as infectious complications, mucositis and/or painful skin lesions.

(iv) The presence of radioactive contaminants on the victim(s). A good rule of thumb is that most of the external contamination is removed by simply removing the victim's clothing. Decontamination (washing) of the skin of uninjured persons with external contamination should be completed at the earliest possible time, and prior to hospital admission. Injured persons can be decontaminated at the hospital or clinic once they are medically stable. Identification of the radionuclide(s) involved is important since proper treatment of internal contamination depends on knowing the specific element(s) involved.

The haematopoietic, gastrointestinal and neurovascular syndromes can only occur if there has been significant total body or large volume, partial body irradiation by penetrating radiation (i.e. x-rays, gamma or neutrons). The cutaneous syndrome can be caused by high dose penetrating radiation exposure as well as by beta radiation that is able to penetrate the stratum corneum. Alpha emitters (such as plutonium and uranium) can cause delayed health problems if material is inhaled or ingested, but most alpha particles are unable to penetrate the intact skin.

In any case, when irradiated patients present at a hospital or clinic, it is essential that important information is gathered and documented so that reasonable decisions can be made regarding subsequent care. Knowledge of each individual's estimated total dose, dose rate (i.e., acute, fractionated or protracted) and approximate volume of tissue involved (i.e. total, partial body or small local area of injury) is necessary in making treatment decisions and prognosis. The nature, timing and severity of symptoms and signs, along with common laboratory tests and a history of events indicating that an exposure was possible, can provide not only verification of an exposure, but also an indication of its magnitude.

Consultation with a health physicist, medical physicist or radiation safety officer is recommended anytime a person is injured by ionizing radiation. These professionals may be able to take immediate steps to prevent injury to others. In addition, they can provide verification of the radiation incident, assistance with dosimetry and identification of radionuclides involved, although, accurate physical dosimetry is seldom available in the early period after an incident. During the first 10 days of the Chernobyl accident, for example, all triage and early medical treatment decisions were based on biomedical information, because little physical dosimetry information was available [1].

Chromosome aberration dosimetry, considered by many to be the 'gold standard' of biological dosimetry, is desirable. A heparinized blood sample for this test should be collected as early as possible to ensure that viable lymphocytes are available for study. Results are not available for several days [2]. Other means of estimating dose are necessary in early patient care.

A full blood count (FBC) with differential, repeated several times at 4- to 6-h intervals, provides useful information after an exposure. Lymphocytes are especially sensitive to the effects of ionizing radiation, and the absolute lymphocyte count (ALC) drops soon after an exposure to penetrating radiation. Goans [3] described a simple, quick and cost-effective method for estimating radiation dose in the first 8 h of the ARS. It is based on the well-known Andrews curve that estimates dose range based on a decrease in the lymphocyte count over a 48-h period [4]. Using data from cases in the Registry maintained at the Radiation Emergency Assistance Center/Training Site (REAC/TS) in Oak Ridge, TN, USA, Goans determined lymphocyte depletion kinetics for x-ray, gamma and mixed gamma-neutron exposures [5,6]. Dose estimates require two or more ALCs, spaced at 4- to 6-h intervals. The dosimetry technique is intended for use as an approximate guide for medical care until more precise dosimetry is available. The procedure has been incorporated into the triage and assessment tool used by the US Armed Forces Radiobiology Research Institute (AFRRI) [7,8].

Subsequent FBCs with differentials, performed throughout the course of the ARS, will provide more definitive information about the radiation dose and the effects of treatment on the haematopoietic system

[2–4,9,10]. Blood counts on patients presenting ≥2 weeks after a significant exposure to penetrating radiation will reveal some measure of lymphopenia, leukopenia and thrombocytopenia. At later times, anaemia will also be evident.

A second, quick way to make an approximate estimate of dose is based on the fact that most individuals (80–100%) with total body exposures >3.5 Gray (Gy) will vomit [11]. The time to emesis has long been recognized as a general indicator of the severity of an acute radiation dose: the higher the dose, the sooner the victim vomits. Goans [3] has graphed the relationship. Many recent publications provide tables with estimates of severity of exposure based on time to vomiting [2,12]. It is important to note, however, that vomiting could be delayed in a high dose, protracted exposure (see Table 2).

Data from accident and therapy patient(s) [1,13,14] have shown that an elevated temperature soon after irradiation is related to radiation dose. Hartman and Bojar report an elevated temperature >37°C within 5 h of a total body irradiation is related to a radiation dose of ≥2.5 Gy [13]. An elevated temperature after the prodromal period is likely to be related to infection, dehydration or other problems.

Serum amylase values can be useful in the early verification of a radiation exposure, although only very general estimates of the severity of the exposure can be made due to the great variability in normal values [15]. Parotitis is not uncommon after a total body or large volume partial body irradiation if the salivary glands are in the radiation field. Elevated serum amylase levels have been documented in both accident and therapy patients [1,15–18]. Doses to the parotids >0.5 Gy cause a significant increase in serum amylase [15]. In the Tokaimura criticality accident, for example, the serum amylase level for the most seriously injured patient rose from an initial measurement of 176–2143 IU in a 15-h period [19].

Assessment of the condition of the skin and oral mucosa is important after an exposure incident. Erythema may or may not be present, but if present, its location should be documented. This will aid in determining the areas involved and the uniformity of exposure. Widespread, early erythema (occurring in <6 h after exposure) could herald development of the cutaneous syndrome. In incidents involving explosions, it is necessary to distinguish between flash and/or thermal burns and erythema caused by high radiation doses [20]. Erythema of mucosa portends development of radiation mucositis or 'the oropharyngeal syndrome' [1].

The use of several methods to verify and assess radiation injury is recommended in all cases. It is important to

Table 2. Prodromal phase of ARS

Symptoms and medical response	ARS degree and the approximate dose of acute whole-body exposure (Gy)				
	Mild (1–2 Gy)	Moderate (2–4 Gy)	Severe (4–6 Gy)	Very severe (6–8 Gy)	Lethal (>8 Gy)
Vomiting onset	2 h after exposure or later	1–2 h after exposure	Earlier than 1 h after exposure	Earlier than 30 min after exposure	Earlier than 10 min after exposure
Percentage of incidence	10–50	70–90	100	100	100
Diarrhoea	None	None	Mild	Heavy	Heavy
Onset	—	—	3–8 h	1–3 h	Within minutes or 1 h
Percentage of incidence	—	—	<10	>10	Almost 100
Headache	Slight	Mild	Moderate	Severe	Severe
Onset	—	—	+24 h	3–4 h	1–2 h
Percentage of incidence	—	—	50	80	80–90
Consciousness	Unaffected	Unaffected	Unaffected	May be altered	Unconsciousness (may last for seconds/minutes)
Onset	—	—	—	—	Seconds/minutes 100 (at >50 Gy)
Percentage of incidence	—	—	—	—	
Body temperature	Normal	Increased	Fever	High fever	High fever
Onset	—	1–3 h	1–2 h	<1 h	<1 h
Percentage of incidence	—	10–80	80–100	100	100
Medical response	Outpatient observation	Observation in general hospital, treatment in specialized hospital if needed	Treatment in specialized hospital	Treatment in specialized hospital	Palliative treatment (symptomatic only)

Used with permission: IAEA [12].

remember that intense anxiety can cause symptoms similar to those of the prodromal period, but rising temperature and frequent vomiting are not likely to be due to anxiety. Clinical signs and symptoms, combined with laboratory findings of a falling lymphocyte count, should be sufficient to make a diagnosis of ARS. Evidence of an early elevated temperature, combined with a rising serum amylase, in a patient with conventional trauma or burns and a history of possible irradiation could mean that the patient also has the ARS. This could be helpful information if the FBC results are not useful because of changes that occur with trauma, because transfusions were utilized in emergency care or because dosimetry is not readily available. Serum amylase measurements may not be useful if conventional trauma involves the parotids or the pancreas. Analysis of amylase isoenzymes may be helpful with the differential diagnosis, since the parotid fraction is elevated with radiation exposure [16,17].

A publication by Fliedner and the 'Metropol' team of authors offers considerable information and guidance regarding assessment of the irradiated patient [10]. It focuses on establishing a 'response category' for each patient based on haematological parameters, neurological, gastrointestinal and cutaneous symptoms and their severity and organ specific grading, with the intent to guide clinical management and prognosis. Completion of the requested documentation regarding a radiation accident patient would provide a 'framework for comparisons of doses, morbidity, mortality and treatment outcomes on an international basis for persons exposed to ionizing radiation' [21].

Current procedures for triage and assessment in a mass-casualty situation have been prepared by AFRRI and REAC/TS and are available on their websites [7,20]. In addition, the International Atomic Energy Agency (IAEA) has prepared guidelines for assessment and treatment [12].

Therapy in the prodromal phase

Patients with combined injuries should have serious trauma or burns evaluated and treated promptly according to conventional protocols. Necessary surgery should be completed within 24–36 h of exposure [22,23]. All blood or blood products used should be leukoreduced and irradiated to 25 Gy as a means of minimizing the risk of developing graft-versus-host-disease [2]. Once patients are stable, they should be assessed and treated for the ARS. These patients will become pancytopenic and immunocompromised, and healing of wounds will be delayed. Prognosis is generally poor for patients with combined injuries. Survival depends upon the type and severity of trauma, as well as upon the radiation dose.

Irradiated patients without trauma or burns might require treatment for nausea and vomiting, diarrhoea, pain, fluid and electrolyte losses. Psychological support will be needed by most patients and their families. 5HT-3 receptor antagonists such as granisetron, tropisetron, ondansetron and dolasetron are most effective for vomiting, although conventional antiemetics might be effective for those with lower radiation doses. Neurokinine-1 receptor antagonists are a new class of antiemetics that have been used in combination with 5HT-3 receptor antagonists in chemotherapy, but published information about the use of this combination in radiation therapy or accident patients is not available [24].

Loperamide, anticholinergics or Amphogel® can be utilized for the treatment of diarrhoea [9,10]. Alosetron, a 5HT-3 antagonist used for irritable bowel syndrome, is not recommended for gastrointestinal syndrome because it is associated with colonic ischaemia [25]. Headache can be severe with high radiation doses. It can be treated with conventional agents, although some caution that the use of aspirin can lead to bleeding [10]. Fatigue, a universal and persistent symptom after a significant exposure, has been a subject of study, particularly by the military. Its cause and remedy have not been determined.

Assessment and therapy in the latent and manifest illness phases

Except in special circumstances, treatment for radiation injury is not likely to be needed for patients having doses <1 Gy. Victims of a mass-casualty incident having estimated doses >10 Gy, and those with serious combined injuries, should have supportive care [2]. If resources are available or if transfer to an unaffected hospital can be arranged, additional treatment can be provided. It is worth noting that many individuals seeking medical attention following a nuclear or radiological incident would not actually have been exposed to a significant radiation dose [26]. Psychological support should be available for these individuals.

Assessment of the patient is an ongoing task throughout the course of the ARS. It should include both the physical state of the patient and re-evaluation of dosimetry as new information and/or expert assistance becomes available. A complete history and thorough physical exam should be accomplished in order to identify pre-existing disease and factors affecting survival. Blood and tissue typing are recommended in the event that stem cell, platelet or RBC transfusions are needed [10].

Patients with a total body exposure >1 Gy will develop dose dependent, increasingly severe aspects of the haematopoietic syndrome. With significantly higher doses, the gastrointestinal, neurovascular or possibly the cutaneous syndromes will be present along with the haematopoietic syndrome. Symptoms of these syndromes will be evident before pancytopenia develops.

Therapy for the ARS patient is directed to prevention of and, if necessary, treatment of infection; stimulation of the production of new blood cells to replace those lost

through natural attrition and injury; replacement of lost cells when necessary (i.e. transfusions of platelets, RBC, stem cells); provision of supportive therapy (nutrition, hydration, pain control, psychological support, etc) and treatment of skin injuries. Because ARS victims will lose white cells and be immunocompromised, a protective environment is recommended during their treatment. Standard medical, nursing and dietary procedures for managing the pancytopenic, immunocompromised patient should be instituted.

Prevention and treatment of infections

Recovery from the haematopoietic syndrome is dependent upon the ability to prevent or successfully treat infection in the immunocompromised patient. Depending on dose, the nadir of the leukocyte count is not reached for a matter of days to weeks after a victim is irradiated. This delay allows time to clear up existing infections, close skin wounds and treat mucositis prior to the onset of neutropenia. Most organisms are acquired from food, water and air, so precautions with food and water, restriction of contacts, use of laminar airflow or other controlled ventilation rooms, a protective environment and restriction of invasive procedures are desirable.

Herpes virus reactivation is common in the ARS patient, and it is frequently manifested early in the immunocompromised host. Patients seropositive for cytomegalovirus infection can be given prophylaxis and/or treatment with ganciclovir or related agent.

The severity of an infection in the ARS patient is dependent on the virulence of the infectious agent, the number of infectious organisms, the humoral and cell-mediated responses of the body and the presence of sufficient and effective phagocytic action within the body. The absolute neutrophil count is the most important and readily available measure of susceptibility to infection. Extreme neutropenia with absolute neutrophil counts of 500 cells/mme3 (0.500 $\times$ 10e9 cells/l) predicts impending infection. Febrile neutropenic patients require immediate intensive antibiotic treatment [27].

Recommendations of the Strategic National Stockpile Radiation Working Group (USA) specify the use of broad-spectrum prophylactic antimicrobial agents during the potentially prolonged neutropenic period. Fluoroquinolones are recommended for this purpose, along with penicillin or streptococcal coverage. If fever develops, the fluoroquinolones should be discontinued and parenteral gram-negative coverage should be implemented [2]. Treatment guidelines for the neutropenic patient are available from the Infectious Disease Society of America [27,28].

Once immunosuppression and leucopenia are present, there is a significant chance of oral candidiasis. Prophylaxis and/or treatment can be accomplished with fluconazole daily by mouth. Should aspergillus infection develop, a triazole such as voriconazole may be needed. Invasive aspergillosis or candidiasis may require the use of caspofungin, an echinocandin [29].

Infections are a significant problem in the gastrointestinal syndrome. Loss of the mucosal barrier allows translocation of commensal bacteria to the liver and spleen, with the possibility of a fatal septicaemia. Quinolone antibiotics have been effective in controlling these systemic infections because of their ability to eradicate species of Enterobacteriaceae. Quinolone-resistant organisms of the species Streptococcus may cause secondary infections.

Antibiotic use in radiation injuries and illnesses is problematic because of the uncertainty regarding the organisms affecting a patient, the drug resistance of organisms and the uncertainty about the individual's immune status. Even after marrow or stem cell transplants, cytokine use and apparent recovery of adequate numbers of leukocytes, immune function may still be impaired [30].

Stimulation of new cell production

Bone marrow throughout the body has the capacity to produce new blood cells, provided it contains surviving haematopoietic stem cells, suitable stromal environment and the proper stimuli for cell production. Most radiation accidents cause non-uniform exposures with variable doses to haematopoietic production sites in the body, and thus survival of some stem cells and differentiating cells. In addition, current research indicates that subpopulations of stem cells have differing sensitivities to radiation, with some populations being less radiosensitive than others [31].

Based on experience in radiation oncology, haematology, limited radiation accident experience and market availability, recombinant forms of granulocyte colony stimulating factor (G-CSF, filgrastim), granulocyte-macrophage colony stimulating factor (GM-CSF, sargramostim) and pegylated G-CSF, (peg G-CSF, pegfilgrastim) are recommended for radiation-induced neutropenia or aplasia. Although not approved by the US Food and Drug Administration for the treatment of radiation-induced neutropenia, the rationale for use of the colony stimulating factors is clear. These haematopoietic growth factors decreased the period of neutropenia in the limited number of radiation accident victims studied, enhanced neutrophil recovery in cancer patients and caused improved survival in irradiated animal models. These cytokines are also able to activate or prime neutrophils to enhance their function [2].

Treatment with a haematopoietic growth factor (GM-CSF, G-CSF or peg G-CSF) is recommended with radiation doses between 3 and 10 Gy, or as soon as the

definite fall in the ALC below baseline (~2000 lymphocytes) and a continued fall in follow-up of ALCs is noted. Growth factor treatment should be initiated in the first 24 h for optimal efficacy. For information on dose regimens of special groups such as children and pregnant women, see Waselenko *et al.* [2].

Haematopoietic growth factors have also been developed to stimulate the production of megakaryocytes. Interleukin-11 is the only one of these currently being used [32,33]. Erythropoietin has not been used in radiation accidents. Thrombocytopenia and anaemia can be significant in ARS patients and can be life threatening if radiation doses are high, if there are combined injuries or if the cutaneous syndrome is present.

The discovery and development of growth factors and other cytokines for human use is an active, extremely complex, challenging area of research that holds much promise for the future. Numerous agents have shown considerable promise in aiding recovery of the haematopoietic system in animals, but further study is necessary to identify all the target cells for a cytokine molecule, to determine the action of the molecule on each type of receptor and to ensure safe use in humans.

Management of gastrointestinal injuries

The rapidly dividing epithelial cells that produce the mucous barrier lining the mouth and oropharynx are radiosensitive. Mucositis occurs when there is loss of the mucous barrier and underlying cells because of radiation exposure, resulting in very painful lesions of the mouth and oropharyngeal tissues that last for weeks. This affects the patient's ability to eat, swallow, talk and has a considerable psychological impact. Most importantly, the denuded areas provide a portal to infectious agents.

Antibiotic administration does not prevent severe radiation-induced mucositis [34]. Research has shown that GM-CSF (topically or subcutaneously) does not relieve the symptoms [35,36]. Sucralfate mouthwash has been shown to be of benefit in decreasing the sensitivity and discomfort [37]. Repifermin and palifermin [both recombinant human keratinocyte growth factor (KGF)] have shown promise in reducing the duration and severity of mucositis in radiotherapy patients when given prior to or after therapy [38,39]. Their use in accidents has not been documented. Sharp [40] has pointed out that the use of haematopoietic growth factors has incidental beneficial effects on mucositis and the gastrointestinal (GI) syndrome, because the increase in neutrophils is associated with a decrease in infections.

The effects of a significant irradiation (>9 Gy) of the abdominal area vary with time. Minutes to hours after exposure, symptoms include nausea, vomiting, diarrhoea and possibly abdominal cramps. Hours to 2 days post-exposure, there is diarrhoea and delayed gastric emptying. Days to weeks later there is persistent diarrhoea, malabsorption, severe fluid and electrolyte imbalances and septicaemia [41]. The prognosis associated with the GI syndrome is poor.

Neurogenic disruptions and the release of serotonin and other chemical signals alter gastrointestinal motility, secretions and contractile behaviour shortly after a radiation exposure. Gastric emptying and motility are suppressed while an increase in the incidence of giant retrograde contractions and giant migrating contractions has been shown in dogs. These abnormal contractions are most likely the cause of abdominal cramping after radiation exposure. Orad or aborad propulsion of GI contents results in vomiting or diarrhoea [42]. Treatment with 5HT-3 receptor antagonists and loperamide can ease these symptoms in the prodromal period. Diarrhoea occurring during the period of manifest illness can be due to other causes, such as irritation from the release of enzymes and bile salts into the injured intestine [42].

Mitotically active cells of the villi of the small intestine are radiosensitive. Loss of the stem cells of the crypts of Lieberkuhn has been attributed to their rapid turn over rate [43] as well as to microvascular injury associated with radiation exposure [44]. Loss of the mucosal barrier and the normal ecology of colonization resistant flora provide systemic access and an environment for sepsis. Septicaemia, as well as ulceration, necrosis, haemorrhage and multiple organ failure have led to death in accident victims suffering the GI syndrome [1]. Treatment options are limited at this time. Oral recombinant intestinal trefoil factor has been shown to aid recovery from intestinal mucositis in mice [45]. Numerous other agents such as KGF, transforming growth factor beta-3 and interleukin-11 have shown benefit if administered prior to, but not after exposure [43]. Consultation with a radiation or medical oncologist is recommended in making treatment decisions regarding these problems.

A decrease in plasma citrulline concentration has been identified as a marker of mucosal and villus atrophy in patients receiving fractionated radiotherapy [46].

Accident patients with the ARS rapidly lose weight. Maintaining an anabolic state with good nutrition is essential for recovery. Enteral feeding should be implemented at the earliest possible time to prevent respiratory infections, and to preserve muscle, normal protein synthesis and function of all organ systems. The desirable route is oral, but feeding via tube to the duodenum may be necessary. An elemental diet with simple sugars, small peptides, vitamins and minerals (such as Vital HN® or Vivonex®) is recommended. The addition of glutamine to the diet has been suggested, but its use remains controversial because some studies show that it provides no benefit [47]. The addition of probiotics might be beneficial, but data from humans are not available [23]. Parenteral administration of fluids and electrolytes might be necessary to meet bodily requirements.

Haematopoietic cell replacement therapy

The loss of rapidly dividing, undifferentiated cells of the bone marrow results in deficiencies in all the formed elements of the blood. Haematopoietic stem cells are available for replacement from bone marrow donor, peripheral blood (PB) or umbilical cord blood. Stem cell transplants are commonly used in haematology and oncology. Serious radiation accidents are rare and there has been little experience with stem cell replacement for accident victims. Chernobyl and Tokaimura accident victims given stem cell transplants had coexisting problems such as trauma, thermal injury, cutaneous syndromes and graft versus host disease (GVHD) that eventually resulted in their deaths, although they did have successful temporary grafts [1,19].

Consideration for bone marrow transplant (BMT) should be for persons whose exposure was relatively uniform and in the dose range of 7–10 Gy. In most cases, persons with serious trauma or thermal injury should not be candidates for BMT [2]. Bone marrow from a human leukocyte antigen (HLA) identical sibling or family member is preferable for a stem cell transplant, but often is not available. A search for a non-related matching donor is time consuming. Fliedner has defined the target dose of CD34+ bone marrow cells for engraftment of an HLA-matched allogenic BMT in the recipient as $3 \times 10e6$ CD34+ cells/kg body weight [48]. Attempts to stimulate production of cells with G-CSF shortly after a BMT appears to increase the risk of GVHD [49].

PB stem cells can be mobilized in an HLA-matched donor by pre-treatment with growth factor (G-CSF) prior to harvesting. The mobilization process requires ~4 days, but once PB is infused, engraftment and haematopoietic recovery occurs faster than with a BMT. PB grafts provide 10 times more T and B cells than marrow grafts, and as a result, PB recipients have fewer infections than those receiving BMT [50]. AMD 3100, a chemokine receptor antagonist that is still in Phase 1 trials, appears to induce rapid mobilization of CD34+ within hours of its administration, with minimal side effects [51,52].

Umbilical cord blood is readily available, and acquiring it presents no risk to the donor. The recipient's risk of developing GVHD from a cord blood stem cell transplant is low, even with some HLA mismatch [53]. A cord blood transplant contains a relatively small number of cells available for transplant, and this is a distinct disadvantage. In addition, engraftment takes longer. Davey has documented an average of 28 days for engraftment in children given cord blood, with a range of 11–60 [54].

Transfusions of platelets are frequently needed for the patient with the ARS. Physicians treating Chernobyl victims pointed out that 'the degree of thrombocytopenia is a more critical determinant of haemorrhage that previously believed' [55]. They caution that low platelet counts are especially problematic when patients have the cutaneous syndrome or thermal trauma. Anaemia also becomes a problem in patients with extensive skin involvement. All platelet and packed cell transfusions administered to ARS patients must be leukoreduced and irradiated to 25 Gy [2].

Management of skin injury

Small, local areas of radiation injury to the skin are commonly associated with occupational settings. Local radiation injuries can be caused by high activity sealed sources of gamma emitting radionuclides, such as those used in industrial radiography and radiotherapy, by high activity unsealed radionuclides, such as those used in research and in production of radiopharmaceuticals (such as F-18 fluorodeoxyglucose), as well as by electrical instruments that generate x-rays. Numerous hand and finger injuries have been caused, for example, by failure to de-energize x-ray crystallography, fluorescence spectroscopy, diffraction spectroscopy and industrial x-ray devices prior to repair. Most local radiation injuries have been caused by mishandled and lost industrial radiography sources.

There are few early signs and symptoms associated with irradiation of small areas of skin, even at high doses. A local radiation injury (such as to a hand) is an extreme example of a non-uniform radiation exposure [56]. An early inflammatory response causing erythema of the skin may be fleeting. At very high doses there may be marked erythema, swelling or even blister formation in the first day of the exposure, but this is uncommon. In many cases, patients are not aware of the injury until weeks after the exposure incident, when oedema (sometimes described as a feeling of tightness, itching or tingling), erythema, changes in pigmentation (tanning of the skin), desquamation, blister formation and pain occur. Thermal, chemical or electrical injury, skin disease, insect bite and allergy should be ruled out. A history of working with radioactive material or x-ray generating devices, or a history of finding and handling an unknown metallic object can be significant. A report of similar symptoms occurring in family members or co-workers could mean that others may have been irradiated in the incident [57].

The pathology of local radiation lesions may show loss of cells of the epidermis and dermis. Depending on the energy of the radiation, the dose and the dose rate, there can also be damage to underlying tissues, with significant, progressive damage to the microvasculature and chronic fibrosis formation. With the exception of superficial injuries, these wounds evolve slowly, heal poorly and are prone to break down, often years later when exposed to physical injury.

Diagnostic and assessment procedures to identify the area of tissue damage, the depth of the injury and the condition of the vasculature and underlying structures (bone, nerves) include thermography, laser Doppler

perfusion imaging, nuclear magnetic resonance imaging, near infrared spectroscopy, ultrasound and serial digital photography [10,58,59]. Serial FBCs are always indicated to rule out a total or large volume partial body exposure. An accident mock-up and evaluation by a health physicist can provide additional information about dose, dose rate and dose distribution.

Treatment focuses on prevention of injury and infection in the involved area, prevention of further vasculature insult, pain control, fostering an acute wound-healing environment and minimizing fibrosis. Recommendations typically include cessation of smoking, nutritional supplements of vitamins A, C and E, use of pentoxifylline to decrease the viscosity of blood and to improve its flow, treatment of infection and, when necessary, careful surgical debridement of devitalized tissue. Various topical drugs such as silver sulfadiazine and steroids are often used for moist reactions. Integra®, a bilaminate skin substitute [60], has been used with success to cover wounds and facilitate formation of granulation tissue in preparation for skin grafting. Recombinant human platelet-derived growth factor (becaplermin) and KGF, not yet approved for radiation injuries, may be used to foster granulation and epithelialization [61]. Hom and Manivel [62] reported the successful use of becaplermin in treating a 12-year-old, previously irradiated problem wound. Milanov advises surgical treatment with aggressive debridement and immediate coverage with well-vascularized skin flaps to provide rapid healing and return of function [63]. Reduction of fibrosis formation in chronic radiation wounds has been achieved with the use of injected interferon gamma [59,64,65].

The cutaneous syndrome that involves an extensive area of skin and possibly deep tissue injury results in systemic problems such as those found with large area thermal burns. The dangers of infection, haemorrhage, anaemia, endogenous intoxication, disseminated intravascular coagulation and multi-organ failure are always present. If a patient has both the cutaneous syndrome and the haematopoietic syndrome, the prognosis is very poor.

Barabonova [56] reported that severe cutaneous syndrome dramatically affected the survival of patients with the ARS following the Chernobyl accident. It was the main cause of death in more than half the lethal cases. Collaboration of haematologists, burn specialists, radiation oncologists, radiation medicine specialists, infectious disease specialists, psychologists and specialists in pain control is needed for the complex treatment of these patients.

Treatment of internal contamination

Internal contamination with radionuclides can occur by inhalation, ingestion, absorption through a wound or intact skin and injection. It is important to treat internal contamination promptly, preferably within the first several hours after exposure. Treatment of life-threatening trauma, however, takes priority. Internal contamination does not usually occur without external contamination being present, except in unusual circumstances (i.e. ingestion of water or foodstuffs contaminated by a malevolent act, or inhalation and/or ingestion of contaminants following a serious reactor or nuclear weapon incident).

Radionuclides react chemically exactly the same as their stable counterparts and therefore the body does not distinguish between one or the other, metabolizing them both exactly the same. Treatment varies with each specific element involved, so it becomes extremely important to identify each contaminant. Identification by bioassay is slow and a specimen can be easily contaminated. Identification by whole-body counting is limited by residual skin contamination, variable chest wall thicknesses and other technical factors.

Careful questioning may result in identification of the contaminant in an occupational setting. In addition, a careful investigation by the health physicist or radiation safety officer will make the identification and/or verify the history provided by the patient. A body survey, to rule out external contamination should be done. Swabs of the right and left nares, nasal blows and sputum samples should be collected in separate containers.

When wounds are found to be contaminated, they should be thoroughly irrigated and cleansed to prevent further radiation exposure and internal absorption. The contamination should preferably be reduced to background levels, but this is seldom possible. Treatment to reduce the retention in the tissues is required.

An estimate of the amount of internal uptake must be made after identification of the specific radionuclide. Small amounts may not require treatment. The annual limit of intake (ALI) is a value that can be determined by the health physicist or radiation safety officer. If the value exceeds the ALI and the patient is a young person, then treatment may be considered. In older persons (>60 years), higher limits may be tolerated.

There are several mechanisms by which various drugs or chemical substances may help eliminate radionuclides. These mechanisms are dilution, displacement, chelation and reduction of absorption from the GI tract. The drugs, doses and methods of administration are well covered in *Management of Persons Accidentally Contaminated with Radionuclides* [66] which was published in 1980 and is currently under revision.

Summary

Early diagnosis and dose assessment are important when persons are accidentally or intentionally injured by ionizing radiation. Administration of haematopoietic growth factors can minimize the period of neutropenia

in the ARS patient. Prevention and control of infection and excellent supportive care are essential to survival. The presence of gastrointestinal and/or cutaneous syndromes increases the chance of significant morbidity and mortality. Replacement of stem cells using bone marrow, PB or cord blood stem cells may benefit selected cases. Immune reconstitution and persistent thrombocytopenia continue to be problematic in treatment, as does the cutaneous syndrome. Nevertheless, current approaches to treatment facilitate survival at doses once thought to be lethal.

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Conflicts of interest

None declared.

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