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Review

Clinical Aspects of Radiation Accident Medical Management

Harald Dörr*, Guennadi Goulko, Viktor Meineke and Harry Scherthan

Bundeswehr Institute of Radiobiology Affiliated to the University of Ulm, Neuherbergstr. 11, D-80937 Munich, Germany

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Radiation accidents, fortunately, are rare events. However, the potential consequences can be very serious and radiation accident medical management is of great importance. In terms of clinical treatment decisions, it is crucial to rapidly obtain an estimate of the exposure scenario to predict the expected severity of radiation-induced injuries and to manage medical treatment. Accident scenarios involving dispersion of radioactive materials or nuclear power plants can mount up to large-scale events, like the accidents at Chernobyl and Fukushima. Thus, preparatory planning of the medical management of radiation accident victims is very important. Different types of radiation exposure, sometimes combined with injuries are possible and the diagnostic and therapeutic measure as well as the outcomes will accordingly differ. The absorption of significant doses of ionizing radiation will lead to acute radiation syndrome (ARS) whose clinical course depends on the absorbed radiation dose and its distribution. Besides the hematopoietic system being the most vulnerable organ system to radiation exposure, the skin plays an important role in diagnostics and treatment of radiation accident victims. Multi-organ-involvement and multi-organ-failure also need to be taken into account. Basics and principles of radiation accident medical management and the most important therapeutic approaches will be addressed.

Key words: decorporation therapy, incorporation, medical radiation accident management, radiation syndrome

1. Introduction

Radiation accidents are fortunately rarely encountered, however, the potential consequences of large-scale accidents can be very serious, like in the radiation accidents of Chernobyl and Fukushima or the Goiania accident in Brazil. Thus, radiation accident medical management for the seriously exposed individuals is of great importance to reduce and mitigate the potential damage, which, as a key step, requires preparatory planning[1]. Acute and chronic health impairment, psychological reactions and considerable direct and indirect economic damage are among the potential consequences of radiation accidents[2, 3].

In terms of clinical treatment decisions, it is crucial to rapidly obtain an estimate of the exposure scenario to predict the expected severity of radiation-induced injuries and to manage medical treatment. Accident scenarios involving nuclear power plants (NPP) or dispersion of radioactive material can mount up to large-scale events Ionizing radiation (IR) accident patterns largely fall into the category of partial body irradiation with an inhomogeneous field distribution, while rather homogeneous total body irradiation has rarely occurred

Harald Dörr: Bundeswehr Institute of Radiobiology Affiliated to the University of Ulm
Neuherbergstr. 11, D-80937 Munich, Germany
E-mail: haralddoerr@bundeswehr.org

in reported radiation accidents and largely resulted from radionuclide incorporation[4].

Radiation accidents can range from a few up to several hundreds or thousands of persons involved, depending on the type of accident and the amount of released radioactive material and doses involved. External radiation exposure can occur, e.g., from an abandoned or stolen radiation source. Internal exposure is a consequence of the incorporation of radionuclides. Large scale nuclear accidents like the NPP accidents of Chernobyl and Fukushima can cause a combination of external and internal irradiation. Radiation emergencies can entail the development of acute and chronic health disorders, psychological problems, and considerable direct and indirect economic damage[3].

2. Basics and principles of radiation accident medical management

In the case of a radiation accident there is the immediate need to reconstruct the exposure scenario to aid the clinical decision making. Past accidents have shown that in early stages of an accident situation there is only limited reliable information about the radiation dose(s) and biodosimetry data will become available only after days.

Appropriate medical management encompasses a number of significant factors. In addition to the type of radiation accident, the number of people exposed to radiation and the severity of exposure play a particularly important role. Medical treatment for exposed patients differs considerably depending, for example, whether the patients have been exposed to lower levels of radiation (< 400 mSv), or to high IR levels resulting in acute injuries.

Low level radiation exposure, due to dispersion of radionuclides, e.g. in a NPP accident, can easily affect a large number of people, raising the need for extensive health care actions such as initial evacuation, decontamination, decorporation therapy and the distribution of tablets with stable iodine as a prophylaxis and countermeasure against thyroid exposure due to I-131 incorporation.

Acute exposure to high doses of IR (> 1Gy) at high dose rates, on the other hand, will result in completely different medical problems and therapeutic requirements. Patients exposed to significant doses of IR require immediate, intensive and interdisciplinary medical treatment approaches. In some cases, hematopoietic stem cell transplantation has to be considered and prepared for as an early treatment option. It is also important to take into account that the treatment of acutely irradiated patients will absorb significant medical resources, such as burn units, for several weeks.

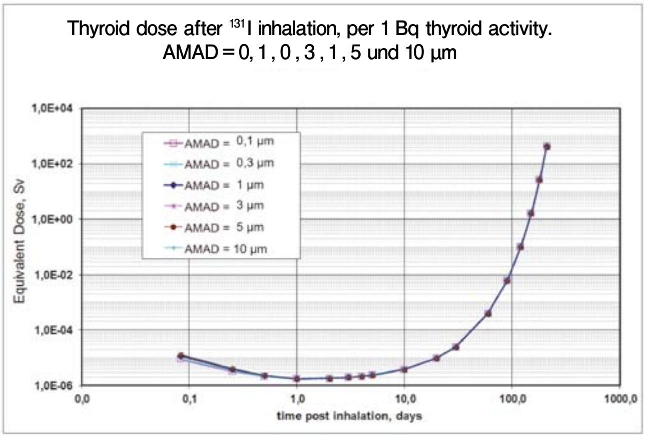
Depending on the scenario, acute or chronic whole body or partial body exposures may be involved. In terms of clinical treatment decisions, it is crucial to rapidly obtain an estimate of the course and geometry of exposure, the radionuclides involved, the exposure pathways and doses / dose rates absorbed to predict the expected severity of radiation-induced damages. In absence of physical dosimetry, biodosimetry tools may provide dose estimations that can support medical treatment planning and resource allocation. However, these assays often require days until results are available[5].

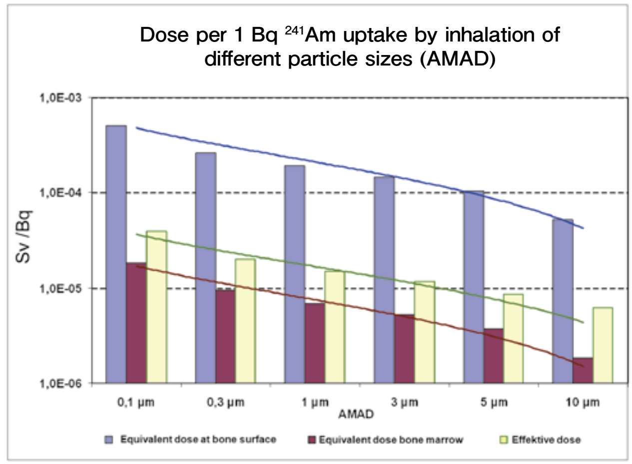
Thus, clinical signs and symptoms of the patients will be of great importance to estimate the expected clinical radiation effects and the patients' prognosis. This can for instance be obtained by the METREPOL system[6] according to which the patients' clinical status will be categorized by using organ specific check lists for the four most important organ systems: the neurovascular system (N), the hematopoietic system (H), the cutaneous system (C) and the gastrointestinal system (G). These METREPOL response categories also include prognostic aspects[6]. When reliable information about the physical dose or results from biodosimetry are available, these data will also be integrated in the decision making process according to the principles of evidence-based medicine.

Individualized diagnostic and therapeutic measures for the affected patient(s) are required, which in the case of whole body exposure includes the consideration of multi-organ-involvement and -interactions[7]. Additional conventional trauma-like wounds and burns of individuals, the so-called radiation combined injury, can aggravate the prognosis[8].

Many aspects concerning clinically diagnosing and managing radiation-exposed patients have to be taken in consideration. After significant acute whole body or partial body radiation exposure it is imperative to take appropriate therapeutic measures as soon as possible. The latency of the manifestation of radiation-induced health impairments can be utilized to differentiate acute versus chronic health effects. Above a threshold dose deterministic pathophysiological changes in radiosensitive organs have to be considered, while stochastic effects like tumor formation will occur after a latency phase. Therefore, irrespective of the IR accident scenario all efforts must be made to reduce the individual exposure to ionizing radiation and to reduce the absorbed dose[9].

In a clinical setting the identification of external contamination with radionuclides is imperative, since in this case first responders, medical personnel, facilities and equipment have to be protected from the spread of secondary contamination. Depending on the size of the radiation accident diagnostic and therapeutic resources on the national level may be challenged or even become exhausted. In the latter case international networks such





(A) (B)

Fig. 1. (A) Equivalent dose of the thyroid after ^{131}I inhalation per Bq of measured thyroid activity as a function of time and particle size. The latter plays virtually no role, since ^{131}I is highly soluble. (B) Equivalent dose at bone surface, bone marrow and effective dose after ^{241}Am uptake by inhalation of different particle sizes, given per Bq ^{241}Am measured. For this radionuclide, different particle sizes play a role for uptake and dose build up, (AMAD, activity median aerodynamic diameter).

as the Radiation Accident Medical Preparedness and Assistance Network (REMPAN) of the World Health Organisation (WHO) and the Response Assistance Network (RANET) of the International Atomic Energy Agency (IAEA) will be able to support the affected countries (http://www.who.int/ionizing_radiation/a_e/rempan/en/).

3. Therapeutic principles in the clinical management of patients with ARS

Clinically diagnosing and managing radiation-exposed patients will involve many aspects of medical care. After significant acute whole body or partial body radiation exposure, it is imperative to rapidly take appropriate therapeutic measures. Clinical management of patients with ARS is characterized by dealing with radiation-induced impairments of different organ systems, multi-organ interactions or even multi-organ-failure. The most critical and most vulnerable organ-system to radiation exposure is the hematopoietic system. The impairment of the hematopoiesis will result in pancytopenia of various degrees with consecutive increased risk of infection, hemorrhage and anemia. General medical management consists of barrier nursing conditions, sufficient and immediate therapy of infections and/or prophylactic administration of antibiotic, antimycotic and antiviral substances.[6, 10, 11)]

Upon increasing degrees of impairment of the hematopoetic system the main therapeutic approaches will be the supply of blood products such as erythrocyte concentrate, the administration of cytokines like granulocyte colony-stimulation factor and granulocyte-macrophage colony-stimulating factor and even the transplantation of hematopoetic stem cells[12)].

The diagnosis whether or not an autologous recovery of the hematopoiesis can be expected or whether there is demand for hematopoietic stem cell transplantation requires specific expertise. It has to be realized that there is only a narrow range between beneficial treatment with hematopoietic stem cell transplantation on one hand and a very poor prognosis due to radiation effects in other organ systems or even multi-organ-failure on the other hand[13-16)].

Besides internal organ systems, there is an important role of the skin in the medical diagnostics and treatment of patients with ARS and local radiation injuries. The impairment of the skin can be challenging in the clinical management of patients with cutaneous radiation syndrome (CRS), because of impaired barrier function and the resulting inflammatory reactions[17)]. Therapeutic principles in the clinical management of patients with CRS include a spectrum of conservative methods including measures for pain control, reduction of inflammation, prevention of infection and of further vasculature insult, improvement of circulation, healing acceleration, and wound cleaning to minimize fibrosis. If the radiation damage leads to the development of necrosis in larger areas, surgical treatment and skin grafts are required[18)]. More recent approaches include the administration of mesenchymal stem cells and have shown promising results[19, 20)].

Table 1. Radionuclide decorporation therapy for selected nuclides

Radionuclide	Decorporation agent	Mechanism	Route of administration
^{60}Co	Ca-DTPA, Zn-DTPA	Chelating agent	intravenous
	Na-EDTA	Chelating agent	intravenous /intramuscular
^{90}Sr	Barium sulphate	blocks intestinal absorption	orally
	Aluminium hydroxide		
	Calcium carbonate	competes for bone binding	
	Calcium phosphate	Increases excretion	
^{131}I	Potassium iodide	Blocking of thyroid	orally
	Sodium perchlorate		
^{137}Cs	Prussian blue	Inhibition of enterohepatic recirculation	orally
^{241}Am	Ca-DTPA, Zn-DTPA	Chelating agent	intravenous
^{235}U	Sodium bicarbonate	protection of kidneys from U deposition	intravenous
^{210}Po	Dimercaprol (BAL)	Chelating agent	intramuscular
	D-Penicillamine		orally

For further information see Refs[23, 29]

4. Contamination and incorporation of radionuclides

The identification of an external contamination is of great importance, since the appropriate decontamination has to be carried out as soon as possible[1]. In addition, special precautions need to be taken to protect first responders, medical personnel, facilities, and equipment from contamination. After the accidental intake of radionuclides it is important to aid the medical management and decorporation measures by, e.g., the use of a medical decision support system that provides information on the radionuclide(s) involved and allows for dose reconstruction and assessment. Identification of the radionuclide(s) has to be the first step, since the decorporation therapy will be adapted to the isotopes encountered (e.g., Farina *et al.* 1991)[9].

It will be of great benefit to obtain an estimation of a particular organ or whole body dose based on the amount of activity of the incorporated isotope. This can be obtained by specific measurements in the whole body or excreta (urine or feces) and ideally will implement personal data (e.g., age, gender), intake route and course (e.g., inhalation, ingestion, wound), intake scenario (acute, chronic), bioassay data (probe type, measured activity) and the nuclide solubility in the body and organ systems (e.g. bone marrow, lung, thyroid; Fig. 1)[21]. Thereby, these data will guide the specific decorporation therapy that has to be initiated rapidly to reduce the resulting internal radiation exposure for the different organ systems. For this purpose an assessment and documentation system has been developed to support the rapid assessment of internal exposures and to assist in decision making[22] where the dose evaluation(s) may be realized with the help of simple figures or tables[23].

For the identification of radionuclides high resolution gamma-spectrometers are the prime choice, in addition to the conventional radiation detectors. As soon as the involved radionuclides are identified, the decision about decorporation therapy (Table 1) will be made. The latter will be based on the radionuclide and the estimated intake and the resulting effective radiation dose[23]. To be able to initiate a specific decorporation therapy instantly, stockpiling of all necessary pharmaceuticals and accessories is of great importance[24].

5. Preparatory planning

In order to reduce potential secondary damage to persons affected by the radiation accident, organizational measures at the exposed site(s) and medical treatment options should be thoroughly planned in advance. The most significant problems in radiation accident management are diagnosing radiation-induced health damage, determining the cause and identifying the radiation sources involved, identifying the non-exposed but worried individuals ("worried-well"), dealing with contamination/incorporation, and treating the patients suffering from acute radiation syndrome.

Preparatory planning should be based on the analysis of possible radiation accident scenarios and previous accident scenarios with their specific causes and effects. Such scenarios range from the release of small quantities of radioactive substances to uncontrollable chain reactions of various dimensions[1]. In addition, the assessment of the risk of terrorist use of radioactive substances has adjusted, particularly since the attacks of 11th September in the USA[25]. After these attacks increasing attention has been devoted to preparatory planning to the threat posed by so-called "dirty bombs" (explosive devices used to disperse radioactive material)[26].

6. Training of first responders and personnel involved

Because nuclear and radiological scenarios, involving e.g. dirty bomb, nuclear accidents, orphan radiation sources, improvised nuclear devices (INDs), may occur in various environments they may lead to a large number of potentially but not physically affected individuals ("worried wells"), representing a challenge for the medical management. The course of past radiation accidents has shown that often only a fraction of the individuals at the site were actually exposed or contaminated, with the majority of individuals being not affected at all. To identify such "worried well" persons and separate them from the ones in need of medical treatment, it is important to train medical personnel and first responders appropriately. Such training will allow early identification of IR-induced injuries in accident scenarios and allow physicians to include them into their differential diagnosis, particularly if patients present with ambiguous skin conditions. For this purpose, all medical personnel who may potentially be involved in the treatment of radiation-exposed patients should receive basic training that enables them to identify radiation-injured individuals at an early stage to ensure appropriate diagnosis and therapy. In the Brazil accident in Goiania, for instance, the local institutions involved had appropriately trained personnel on site who identified exposed patients and administered effective treatment[27].

7. Conclusions

Radiation accident scenarios and past accidents have revealed a spectrum of possible radiation-induced effects, involving a wide range of the number of potentially affected persons.

The principles in radiation accident medical management are similar for different accident scenarios, but limited resources may pose a problem in large-scale events. In such scenarios the availability of required resources can rapidly become a limiting factor for the medical management of the victims. Hence, stockpiling of essential pharmaceuticals for prophylaxis or treatment of affected individuals on a national or international level may be considered.

Prospective clinical studies for the development of new therapeutic measures for patients presenting ARS are extremely limited. Most of the novel medical treatment approaches are derived from experimental studies in animal models. Therefore, a multidisciplinary approach based on international cooperation is of prime importance. Insights in new treatment options may be obtained by the comparative analysis of radiation-induced effects in different animal models with respect to clinical data from radiation accident victims. Modeling of the outcomes on an international scale may be a future approach for identifying new treatments[28].

International networks can provide specific expertise as well as trained personnel and materials resources. There are a few world-wide institutions that are active in the field of radiation accident management and treatment of radiation-exposed patients, and encourage cooperation, such as the REMPAN network (http://www.who.int/ionizing_radiation/a_e/rempan/en/). The exchange of experience allows countries to compensate for unavailable resources. This will also be important in the case of a large scale radiation accident that can exhaust existing national resources. International exchange and support will furthermore require legal mutual agreements to be able to rapidly and efficiently deploy specialists to assist in radiation accident medical management.

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