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The acute radiation syndrome—need for updated medical guidelines

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Abstract

The major immediate and severe medical consequences in man following exposure to high doses of ionising radiation can be summarised within the concept of the acute radiation syndrome (ARS). In a dose-dependent fashion, a multitude of organ systems can be affected by such irradiation, presenting considerable medical challenges to treating physicians. Accidents or malevolent events leading to ARS can provoke devastating effects, but they occur at a low frequency and in a highly varying manner and magnitude. Thus, it is difficult to make precise medical predictions and planning, or to draw conclusive evidence from occurred events. Therefore, knowledge from on-going continuous developments within related medical areas needs to be acknowledged and incorporated into the ARS setting, enabling the creation of evidence-based guidelines. In 2011 the World Health Organization published a first global consensus on the medical management of ARS among patients subjected to nontherapeutic radiation. During the recent decade the understanding of and capability to counteract organ damage related to radiation and other agents have improved considerably. Furthermore, legal and logistic hurdles in the process of formally approving appropriate medical countermeasures have been reduced. We believe the time is now ripe for developing an update of internationally consented medical guidelines on ARS.

1. Introduction

The acute radiation syndrome (ARS), sometimes denoted as radiation poisoning, radiation sickness or radiation toxicity, is a key concept when dealing with medical consequences of radiation exposure. A common definition of ARS is presented by Wikipedia: 'A collection of health effects that are caused by being exposed to high amounts of ionizing radiation, in a short period of time' [1]. A more wide-ranging characterisation is provided by the International Commission of Radiological Protection: 'A spectrum of responses involving deterministic haematopoietic, gastrointestinal, cardiovascular, and central nervous system reactions to a large radiation dose received acutely or sub acutely to all or most of the body' [2]. Radiation can be delivered through an external source, without direct contact with the exposed individual, or through direct contamination, i.e. with radioactive material deposited on external parts of the body (skin, hair, eyes, clothes) or taken into the body through inhalation, ingestion or open wounds. The absorbed dose, dose rate and the radiation quality determine the time from exposure to clinical onset of a range of signs and symptoms, that can ultimately lead to death within hours or up to several months after exposure. An initial clinical 'prodromal' phase is generally followed by a non-symptomatic latent phase, then a period of manifest

illness, eventually succeeded by either recovery or death. Different cell types and organ systems in the body present various sensitivities to ionising radiation. Thus, the threshold whole body exposure doses required to induce clinical organ-related ARS varies, being lowest for the haematopoietic (H) syndrome (approx. 1–2 Gy) and higher for the gastrointestinal (GI) and neurovascular (NV) syndromes (approx. above 6 and 8 Gy, respectively) [3]. High doses are accordingly likely to affect multiple organ systems and therefore risk eliciting multiple organ failure, a dreaded medical condition with dismal prognosis [3].

This special issue of JRP focuses on a multitude of aspects linked to medical management after high-dose radiation exposure. These aspects include discussing the incidence and nature of events leading to ARS, how to diagnose and evaluate the biological, molecular and clinical impact of ARS, as well as late follow-up including lessons learned from earlier radiation events. It also summarises and discusses present, and possible future, medical management of ARS. Here we briefly review recently published recommendations linked to the ARS concept and discuss why there still is a need for an extensive evidence-based international update of medical guidelines aiding the clinical management of this syndrome.

2. Current recommendations

Twenty years ago Fliedner *et al* presented a refreshed view on the medical management of radiation accident victims by introducing a novel 'response category concept'. They scored the severity of radiation exposure and defined diagnostic procedures and therapeutic options in the ARS setting presenting the 'medical treatment protocols for radiation accident victims as a basis for a computerised guidance system' (METREPOL) [3]. The response categories suggested constituted a dynamic ARS clinical scoring scheme, taking into account that estimated organ damage and proposed treatment measures vary as a function of time from radiation exposure. One of the practical limitations of the METREPOL scoring system, however, is that its suggested medical damage categories are not in line with those of another, considerably more widespread system to score adverse events—the common terminology criteria for adverse events (CTCAE) [4]. The CTCAE system is today extensively used in clinical practice worldwide, primarily to score the degree of adverse events related to various therapeutic interventions, in particular for patients with cancerous and infectious disease diagnoses, and it is continuously being updated. Another limitation of employing the recommendations of the METREPOL publication today is, not unexpectedly, that the medical development during the recent 20 years have provided a number of revised and improved medical management options in the clinic. An expanded assessment of the impact and 'legacy' of the METREPOL publication is provided by Herrera-Reyes *et al* in a separate section of this special issue [5].

Several agencies and organisations established by the United Nations are providing publications that include various aspects on the management of the ARS. The International Atomic Energy Agency (IAEA) recently published an update of 'medical management of radiation injuries' in their safety reports series No. 101 [6]. Similarly, the IAEA together with the World Health Organization (WHO) through their emergency preparedness and response—MEDICAL series have issued advice on generic response during a nuclear or radiological emergency [7]. In 2020 an update of this publication was produced specifically targeting medical physicists [8]. The United Nations Scientific Committee on the Effects of Atomic Radiation regularly submits reports including medical aspects on radiation exposure, e.g. their recent 2019 report on sources, effects and risks of ionising radiation [9].

These publications contain massive information, often with particular value on a public health level but are not, however, explicitly aiming at reaching specialised physicians and other health care workers responsible for the medical management of patients encountering the ARS. Thus, other groups have tried to address this issue. The Radiation Emergency Assistance Center/Training Site at the Oakridge Institute in Tennessee has during a number of years provided health care professionals with advice through their publications, courses, web site, and, recently, via a launched app [10]. Another important American resource, managed by the US Department of Health and Human Services and collaborating centres, is the Radiation Emergency Medical Management website and app, with a guidance on diagnosis and treatment for healthcare providers [11]. In Europe, an initiative was taken 2005 by the European Blood and Marrow Transplantation group to gather a large group of international clinical and experimental experts in Paris to formulate a consensus on the medical management of mass radiation accidents. This resulted in an expert review paper [12], followed by a clinically useful two-page 'pocket guide' by the group's Nuclear Accident Committee on the medical management of mass radiation exposure, updated in 2017 [13].

Although these efforts have clearly been incredibly valuable and useful in a clinical setting, attempts to establish extensive modern evidence-based medical guidelines on the management of ARS above the level of expert opinion documents have been scarce.

3. Making the case for an update of current medical guidelines

In a pivotal effort, and adopting modern standards, the WHO Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN) in 2009 set out to generate high-level medical guidance documents providing physicians clinically useful, evidence-based recommendations linked to ARS. A first global consensus meeting was arranged in Geneva with participation from a broad international panel of medical experts and researchers in the field. As an initial step, the group decided to screen available relevant knowledge through an extensive literature review process. This was followed by an evaluation step, where consensus conclusions were agreed upon and subsequent key medical management recommendations were developed and scored. The approach was based on a formalised agenda for creating medical guidelines documents advocated and supported by the WHO, involving application of the Grading of Recommendations Assessment Development and Evaluation system as a crucial component [14]. The whole project work resulted in two peer-reviewed guidelines publications in 2011 [15, 16]. These reports focused on the medical management of health consequences from the haematopoietic and nonhaematopoietic organ systems, respectively, as a result of exposure to high doses of non-therapeutic ionising radiation. Both publications acknowledged the profound lack of clinical evidence to backup proposed medical conclusions and interventions. No randomised controlled clinical trials of medical countermeasures have yet been conducted for individuals with ARS. Clinical data are thus clearly limited and incomplete. Still, the WHO-REMPAN group decided to propose a few general recommendations, based mainly on data generated from managing non-irradiated humans with similar organ toxicities but generated from other agents and from irradiated experimental animals. Among medical countermeasures the group issued a strong recommendation to consider the administration of the growth factors granulocyte- or granulocyte-macrophage colony-stimulating factor (G- or GM-CSF), and a weak recommendation for erythropoiesis-stimulating agents and haematopoietic stem cell transplantation, to improve recovery of a severely damaged haematopoiesis in patients without signs of other severe radiation-induced organ dysfunctions [15].

Developing medical countermeasures for treating severe adverse health effects in patients subjected to large doses of ionising radiation, or other bioterror threats, human challenge studies (exposing people to the threat agent) are generally not ethical or feasible. In such cases the Food and Drug Administration (FDA) may in the US grant marketing approval of medical countermeasures (drugs, biologicals) under the 'animal (efficacy) rule', i.e. approval based on data from well-controlled animal studies establishing that a clinical benefit in humans is reasonably likely. The sponsor of the product must still demonstrate the safety of the product in humans, securing proper risk-benefit analyses. Several drugs have recently been approved by the FDA under the animal rule to boost the bone marrow function and thus to increase survival in patients acutely exposed to myelosuppressive doses of radiation (the haematopoietic syndrome of ARS) following a radiological/nuclear emergency [17]:

- romiplostim (Nplate®), a thrombopoietin (TPO) receptor agonist, in 2021;
- sargramostim (Leukine®), GM-CSF, in 2018;
- pegfilgrastim (Neulasta®), pegylated G-CSF, in 2015;
- filgrastim (Neupogen®), G-CSF, in 2015.

Furthermore, the FDA has several additional new agents with potential medical benefit in connection with high dose radiation exposure (in particular to mitigate effects of internal contamination) listed under 'investigational new drug' status [18].

It is thus obvious that important additional information related to the medical management the ARS has accumulated since the two WHO-REMPAN guidelines reports were published in 2011. There is today a broad international consensus, recently also expressed by ourselves [19], that a comprehensive update of such evidence-based ARS guidelines is highly warranted. The initial, knowledge-screening phase may be aided by the expert-generated information presented in this special issue. Let us do the rest!

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Conflict of interest

The authors claim no conflict of interest.

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