Published in final edited form as:
Stem Cells. 2009 May ; 27(5): 1205–1211. doi:10.1002/stem.16.

Stem Cells, Multi-organ Failure in Radiation Emergency Medical Preparedness: A US/European Consultation Workshop

TM Fliedner, MD[1,*)], **NJ Chao, MD**[2,*)], **JL Bader, MD**[3], **A Boettger Jr, MD**[4], **C Case Jr**[5], **J Chute, MD**[2], **DL Confer, MD**[5], **A Ganser, MD**[6], **N-C Gorin, MD**[7], **P Gourmelon, MD**[8], **DH Graessle, PhD**[1], **R Krawisz**[9], **V Meineke, MD**[10], **D Niederwieser, MD**[11], **M Port, MD**[6], **R Powles, MD**[12], **B Sirohi, MD**[13], **DM Weinstock, MD**[14], **A Wiley, MD**[15], and **CN Coleman, MD**[3]

[1]Radiation Medicine Research Group, Ulm University, Germany

[2]Duke University, RadCCORE Radiation Countermeasures Center of Research Excellence, Durham, NC, USA

[3]National Institutes of Health, National Cancer Institute, Bethesda, MD, and Dept. of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Washington, D.C., USA

[4]Dept. of Radiation Protection, Federal Ministry of Environment, Nature Protection and Nuclear Safety, Bonn, Germany

Address correspondence to: Nelson J. Chao, MD 2400 Pratt St, Suite 9100 Duke University Durham, NC, 27710 Chao0002@mc.duke.edu.

*)Both authors contributed equally to this work.

Author Contributions: Theodor M. Fliedner: Conception and design, administrative support, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript
Nelson Chao: Conception and design, financial support, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript
Judith L. Bader: Collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript
Axel Boettger: Conception and design, financial support, administrative support, data analysis and interpretation, final approval of manuscript
Cullen Case Jr.: Conception and design, provision of study material or patients, collection and/or assembly of data, final approval of manuscript
John Chute: Conception and design, manuscript writing, final approval of manuscript
Dennis L. Confer: Conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, final approval of manuscript
Arnold Ganser: Conception and design, final approval of manuscript
Norbert-Claude Gorin: Conception and design, administrative support, provision of study material or patients, final approval of manuscript
Patrick Gourmelon: Conception and design, administrative support, provision of study material or patients, final approval of manuscript
Dieter H. Graessle: Conception and design, administrative support, data analysis and interpretation, final approval of manuscript
Robert Krawisz: Administrative support, final approval of manuscript
Viktor Meineke: Conception and design, administrative support, data analysis and interpretation, final approval of manuscript
Dietger Niederwieser: Conception and design, administrative support, collection and/or assembly of data, manuscript writing, final approval of manuscript
Matthias Port: Conception and design, final approval of manuscript
Ray Powles: Conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript
Bhawna Sirohi: Conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript
David M. Weinstock: Conception and design, manuscript writing, final approval of manuscript
Albert Wiley: Conception and design, financial support, provision of study material or patients, final approval of manuscript
C. Norman Coleman: Conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript

The views expressed in this paper are those of the authors and do not represent policy of the US government, or Department of Health and Human Services.

[5]National Marrow Donor Program (NMDP), Minneapolis, MN, USA

[6]Dept. of Hematology, Hemostasis, Oncology, and Stem Cell `Transplantation, Hannover Medical School, Hannover, Germany

[7]Dept. of Hematology and Cell Therapy, Hospital Saint-Antoine, Paris, France

[8]Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-aux-Roses, France

[9]American Society for Blood and Marrow Transplantation, Arlington Heights, IL, USA

[10]Bundeswehr Institute of Radiobiology, Munich, Germany

[11]Dept. of Hematology and Oncology, University of Leipzig, Germany

[12]Parkside Oncology Clinic, London, United Kingdom

[13]Addenbrookes Hospital, Cambridge, United Kingdom

[14]Dana-Faber Cancer Institute (DFCI), Boston, MA, USA

[15]Radiation Emergency Assistance Center/Training Site (REACT/TS), Oak Ridge, TN, USA

Abstract

The concern of the public regarding terrorist actions involving nuclear emergencies resulted in the reopening of the discussion regarding the best ways to cope with the inevitable health impairments. Medical experts from the United States and from Europe considered it of importance to harmonize at an international level the diagnostic and therapeutic approaches regarding the radiation-induced health impairments. The present contribution is the result of the first US/European Consultation Workshop addressing approaches to radiation emergency preparedness and assistance, which was held recently at Ulm University, Ulm, Germany. Discussions dealt with the assessment of the extent of damage after total body exposure and, in particular, the quantity and quality of the damage to the hematopoietic stem cell (HSC) pool. Secondly, the pathogenesis of the multi-organ failure was considered because of the organ-to-organ interactions. Thirdly, approaches were considered to harmonize the “triage-methods” used on an international level using the “Response Category” approach as developed for the European Communities. These discussions lead to the conclusion that there is a strong need for continuing education of physicians, nurses and support personnel to address the issues posed by the management of patients suffering from radiation syndromes. Finally, the discussions expressed the need for more international cooperation in research and development of more refined methods to treat patients with any type of radiation syndromes.

1. Introduction

The scope and purpose of this consultation workshop was to bring together a group of experts in the field of the medical management of radiation accident victims to discuss and compare the emergency approaches used in the USA and in the countries of the European Community (EC). There was agreement that there is an urgent need on both sides of the Atlantic to try to achieve a sound and scientifically based harmonisation of efforts and methods regarding the clinical management of radiation accident victims. These methods are critical if there is to be strong and active international cooperation.

Discussions centered on the assessment of the extent of damage after total body irradiation to the hematopoietic damage, especially of the stem and progenitor cell pools as a prerequisite for the decision regarding hematopoietic stem cell transplantation (HSCT). A second topic was related to the fact that any total body irradiation will be the result of the involvement of all cells and tissues on the basis of their biological properties (multi-organ

involvement resulting potentially in multi-organ failure). A third topic arose from the need to have and develop further approaches to determine appropriate “triage” - the prognosis of each of the victims involved as a basis for appropriate therapeutic measures.

Furthermore, these discussions lead to the conclusion – a fourth topic – that it would be necessary and inevitable to review the opportunities for the appropriate clinical training of medical and nursing staff in order to “be prepared” including international cooperation. In addition, there was a consensus on the need for a strong international cooperation in research and development regarding several aspects of radiation emergency medical preparedness and assistance. As such, all these efforts remain a work in progress and will continue to improve as we learn more about possible radiation mitigators, biological indicators of effect and repair and dosimetry as well as shielding efforts.

2. Background: The need to harmonize radiation emergency medical preparedness and assistance at an international level (for background information see references 2, 6, 9, 16, 19, 21, 22, 23, 27, 29, 33, 34, 35, 41)

The citizens as well as the public health and medical communities in the US and Europe remain concerned that our societies are not adequately prepared for large scale criminal or terrorist activities involving radiation. Specialists from the radiation medicine scientific medical community consider it a privilege and responsibility to lead preparedness efforts to provide the best possible care in such acts of terrorism or catastrophic failures [1–9].

Victim care would most likely be coordinated by trauma specialists in close contact with hematology and oncology experts because of their familiarity with hematopoietic toxicities. Although various approaches for optimal treatments have been proposed, there is not complete consensus. Animal models of exposure and countermeasures are helpful but may not be fully applicable to the mass casualty setting, with additional information needed on combined injury of radiation plus physical injury [10–13].

In the United States, the Centers for Medical Countermeasures Against Radiation (CMCRs) within the National Institute of Allergy and Infectious Diseases (NIAID in NIH) is charged with developing novel radiation mitigators and dosimetry techniques. The Department of Health and Human Services, working with interagency partners as well as state and local partners, develops medical response plans. This includes the National Disaster Medical System, the Hospital Preparedness Program and other collaborations with responders and experts from the academic and private sectors such as the National Marrow Donor Program (NMDP), American Society for Blood and Marrow Transplant (ASBMT), Radiation Injury Treatment Network (RITN), American Society of Therapeutic Radiology and Oncology (ASTRO), American Society of Clinical Oncology (ASCO) and others.

In Europe, the EU Commission is authorized to provide only framework regulations for a response. The creation and execution of specific response plans are left to each national government. Thus, there is no overall European plan to create a radiation syndrome oriented uniform policy and no financial means to enhance appropriate medical and response competence in European hospitals beyond what is available on the basis of each country's own risk assessment. However, one professional medical society, the European Group for Blood and Marrow Transplantation (EBMT), an association of more than 400 hospitals in Europe with extensive experience in stem cell transplantation and in treating patients suffering from very severe organ impairments, has established a “Nuclear Accident Committee” (NAC) to develop preparedness research and training programs.

On both sides of the Atlantic, there is a sense of "joint responsibility" to harmonize as much as feasible evidence-based nuclear accident medical preparedness. In this spirit, the US/European Consultation Workshop was conducted at the Science Conference Center of Ulm University "Schloss Reisensburg" to review the "state of the arts" for managing radiation victims. In particular, the purpose of this workshop was to bring together a group of experts in the medical management of radiation accident and terrorism victims to discuss the approaches used based on the European METREPOL Response Category-Grading in Europe and those used in the US, some of which are summarized on Radiation Event Medical Management web site [9, 12].

The Consultation Workshop members recognized that there are major knowledge gaps in understanding the pathophysiology of the acute radiation syndromes (ARS) and the multi-organ dysfunction and failure that can result after significant whole or partial body radiation exposure. It was agreed that new methods for earlier and more accurate diagnosis and treatment of ARS are needed, as well as better radiation mitigators, faster and more accurate biodosimetry tools and a better understanding of partial body shielding effects. This expanded knowledge will assist in the care of victims in both small and large scale events.

The EBMT has developed diagnostic and management guidelines for the clinicians. These efforts were based on the METREPOL concept using the clinical response categories as the basis for clinical decision making [14–15]. This concept is in part available on a web site of the Radiation Medicine Research Group of Ulm University [14]. American proposals were initially developed by the Strategic National Stockpile Working Group [16] and further refined by NMDP and ASBMT working together in RITN (http://www.ritn.org). The current expert-based suggested management algorithms are available on the REMM web site, developed by the Office of the Assistant Secretary for Preparedness and Response, in the US Department of Health and Human Services, in collaboration with the National Library of Medicine (NLM) [1].

The approaches used by EBMT and in the US were felt to be different, but are complementary to each other. The major differences reflected in existing planning and response strategies were based on differences in the types of events being planned for, including differences in

- the exact planning scenario and its location in relation to population centers,
- the type of event (e.g. industrial accident, nuclear reactor meltdown, nuclear detonation) and
- the size of the event (e.g. the kiloton size of an improvised nuclear device).

It was recognized that differences in capacity and capability exist from country to country.

They include the availability of

- medical expertise,
- appropriate biodosimetry tools,
- large scale laboratory facilities and
- specifically designed clinical facilities.

3. Assessment of hematological stem and progenitor cell damage as a basis for planning therapeutic strategies and the use of HSCT

There were extensive discussions on when and how to use HSCs to overcome radiation induced bone marrow failure. A review of the scientific literature, which is historically dated, indicated that this method of treatment has not resulted in significantly improved survival. Future use of HSCT in the management of unintended radiation exposure should follow established guidelines and ensure adequate data collection for evaluation of efficacy. There was a consensus that a HSCT should be considered if the victim's HSC pool is essentially irreversibly damaged (described below) and a suitable donor is available. It may also be considered when victims have reversible HSC injury but would likely succumb to complications of marrow failure before their marrow recovers.

Discussions confirmed that it is currently difficult to determine whether the HSC pool has a chance of autochthonous recovery. A more thorough understanding of the physiology of blood cell formation, its regulatory mechanisms and its repair potentialities is needed. Since the bone marrow in adults is distributed throughout much of the skeleton and the stem cells are able to traffic throughout the body, bone marrow functions as one organ system. Therefore, homogeneity or heterogeneity of total body irradiation as well as the dose and dose rate of exposure plays a major role in the development of the radiation hematopoietic syndrome.

Assessment of the severity of hematopoietic injury by total body radiation exposure requires the use of “indicators of exposure”; “indicators of effect” (and indicators of repair) (see publications of the US National Academy of Sciences). In a radiation accident, experts will provide physical measurements of radiation type, dose and dose rate in the environment. For victims, this needs to be translated into some measure of absorbed dose. The extent of hematopoietic damage after irradiation depends on the structure, function and regulation of the bone marrow, where HSCs are very sensitive to radiation. Animal and human studies indicate that the pluripotent/pluripotent stem cell has a D_0 of about 95 cGy [17]. Therefore, if exposed to a truly myeloablative homogeneous total body exposure of about 6 Gy, one would expect that only 0.25% of cells in the stem cell pool would survive, or only about 2.5 per 1000 cells. This dose would not only produce an arrest in the recruitment of cells from a stem cell/progenitor cell pool, but would also impair and eliminate further proliferation and differentiation of precursor cells. For example, migration of granulocytes from the bone marrow to the circulation would be expected for about 4 days after radiation exposure, since the maturation time of granulocytes in the marrow is about 4 days [18–20]. Thus, after an acute radiation injury one observes prompt emptying of the entire granulocyte marrow reserve, resulting in the remarkable granulocytosis in the first 3–4 days after exposure, with granulocyte concentrations in the blood going up to even 30,000 per mm^3 during the first 4 days, partly driven by systemic endotoxins from GI injury. A granulocyte in the blood has a half-life of about 7 hours (1), and the maximum life span of 24 hours [19]. Thus, after a significant irradiation in humans of 500–1000 cGy, a dose dependent granulocyte overshoot is observed, characteristic of mobilization of a granulocyte reserve. An extensive pathophysiological analysis of the early blood cell changes after radiation exposure is presented elsewhere [21].

There was consensus that HSCT should be considered when the blood cell changes during the first days after radiation exposure are compatible with the severity grade H 4 of the METREPOL approach (i.e., irreversible damage to stem cell pool) [22]. If the constellation of blood cell changes early after exposure indicates the severity code is H 3, H 2 or H 1, then the patient is likely to have a reversible damage to the stem cell pool and should be treated with supportive care to “bridge” the time of temporary hematopoietic failure with

appropriate therapeutic measures. Using mathematical models of granulocytopoiesis, lymphopoiesis and platelet production, a software program is being developed which takes input about radiation-induced early blood cell changes to assign a ”severity of hematologic damage grade”: H1, H2, H3, H4. (28). Medical planning can then be based on the results of this graded output. (These data were presented prior to the workshop and are accepted for publication [23]. In some cases of severe H3, HSCT may also be needed because the patient may succumb to complications before the marrow recovers and HSCT is needed as a bridging technique. Prior to transplant, a bone marrow aspiration and biopsy should be performed from two different marrow sites, ideally in both high and low dose regions, if that information is known, to confirm the status and to assess the likelihood of autologous recovery of the blood cell forming tissue.

Another area of discussion was the bone marrow niche. It is known that the HSCs resides in close association with osteoblasts and sinusoidal blood vessels within the bone marrow and this association contributes to the maintenance of the HSC pool in vivo (31–33). Efforts to improve outcome for affected individuals should also focus on the stem cell niche. Several studies have demonstrated that BM osteoblasts regulate HSC pool size in vivo via the Jagged1-Notch signaling pathway and pharmacologic activation of osteoblasts via treatment with parathyroid hormone (PTH) increases the mobilization of HSCs into the peripheral blood. PTH treatment can also protect BM HSCs from the deleterious effects of repeated cycles of cytotoxic chemotherapy raising the possibility that PTH might be useful in mitigation radiation injury as well (31). HSC and progenitor cells also reside in proximity to BM sinusoidal vessels in the adult, the so called vascular niche (34–37). Exposure to ionizing radiation or chemotherapy induces apoptosis of vascular endothelial cells in vitro and regression of BM sinusoidal vessels in vivo. Ionizing radiation also causes apoptosis of vascular endothelial cells in nonhematopoietic tissues, including the brain and intestinal tract (38–40). BM aplasia and regression of BM sinusoidal vessels developed simultaneously in rodents treated with 20 Gy limb irradiation and more importantly, recovery of hematopoiesis correlated temporally with BM vascular reorganization in vivo. Adult sources of vascular endothelial cells may therefore provide reparative or regenerative signals to BM HSCs which can facilitate hematopoietic recovery following myelotoxicity. Since a subset of BM HSCs are highly radioresistant and potentially responsive to reparative signals from the BM niche, it is plausible that therapies to augment niche activity could accelerate hematopoietic recovery in vivo.

Except in rare instances where autologous HSCs would be available, allogeneic donors–related or unrelated, including cord blood – would be needed. International cooperation to harmonize the necessary approaches and methods of HSCT would be valuable. In the USA, current HLA typing capacity from National Marrow Donor Program is 1000 samples per day. If necessary, buccal mucosa cells can be used to identify the HLA type. It was stressed, that before using a stem cell transplant, the irreversibility of HSC damage should be documented which means that a transplant could not be ready before 14 days following the exposure. Patients with H4 have to receive optimal supportive care, including strict reverse isolation, antibiotics, antivirals, antifungals, platelet and blood transfusion, optimal control of fluid balance etc.). In the case of a large event, international cooperation would be important to optimize capacity.

4. The Acute Radiation Syndromes: The need to replace a mono-organ approach of therapeutic measures by a multi-organ involvement consideration potentially resulting in a multi-organ failure

The METREPOL concept currently uses a multi-organ assessment to characterize clinical effects as a function of time after radiation exposure by grading the severity of effect of the four most relevant organ systems, in particular, the neurovascular system, the hematopoietic system, the gastrointestinal system and the cutaneous system. The grade of the most severely effected organ system defines the “response category” which is used to determine where the patients should be optimally referred to for care. This approach is also helpful to determine the most likely complications to be expected and to select the most appropriate clinical services required.

The Japanese experience in 2 patients of Tokai-mura indicated that all relevant organ systems will show their organ specific picture and pattern of response to radiation [24]. These patients showed in a unique way the course of signs and symptoms as they appear if there is at least a transient recovery of the hematopoietic system. One of them survived for 83 days, the other for 211 days.

In the US/European Consultation Workshop a “unifying hypothesis of the pathophysiology of the radiation syndromes” was presented, suggesting possible future directions for understanding and treating radiation exposed persons [25]. One important feature to be determined and/or developed was how soon after an exposure could the METREPOL be used to determine medical interventions and the use of medical countermeasures. In that the decision to initiate medical countermeasures needs to be made within the first few days for optimal efficacy and there may be tens of thousands of victims requiring triage in a mass casualty event, medical responders need a reasonably accurate system that requires limited data, limited numbers of observations and ease of use. There was agreement in the workshop regarding such a multi-organ failure approach as a potentially useful pathophysiological way for therapeutic actions. Furthermore, it is apparent that the systematic use of such an approach is in itself of importance to initiate appropriate therapeutic approaches since the most important signs and symptoms of the damage caused in the 4 most important organ systems are systematically recorded.

A major part of the workshop dealt with the medical problems to be expected in patients with a potentially reversible damage of the blood cell formation. There was consensus that it was again the pattern of change in the blood cell lineages that dictates to an important extent the clinical course, because blood effects occur at doses generally lower than effects in other organ systems. It is important to realize that the pattern of blood cell changes in patient graded as H3, H2 and H1 follow the same principle. This pattern was observed first in the Oak Ridge patients in 1958 [26]. In these patients (and in all patients observed later exposed in these dose ranges, such as in Chernobyl [27], in some of the Chinese accidents [28], in the Vinca accident etc.) the blood granulocytes show a moderate increase above normal during the first 3–4 days, then a declining tendency reaching granulocytopenic values between 5 and 8 days. Then the concentration remains below normal followed with a stable low count between days 10 and 15 or even a rebound increase (abortive rise). Thereafter a second decrease phase is observed reaching a nadir between days 20 and 30 followed by a spontaneous recovery within days 30–50. Such a course of cell response is seen also in the red cell series (in this case one has to observe the reticulocyte count) as well as in the megakaryocyte-platelet system. These patterns have been described and analyzed with biomathematical tools [29]. The consequences that can be expected after these typical blood cell concentration patterns dictate the clinical measures to be taken: risk of infection during

the time of low granulocyte count, bleeding or even serious blood loss. For all these patients (and in a severe accident situation this may well be possible for the majority of patients) the risk of infection and the risk of thrombocytopenic bleeding is significant.

Extensive discussions were held regarding the role of cytokines in the care of radiation accident victims, especially the hematopoietic syndrome. There was an agreement about the validity of administering selected growth factors only if there was evidence of a cell population of stem or progenitor cells likely to be present, i.e., not H 4 [15]. The group agreed that current management of haematological aspects of ARS does not materially differ from the management requirements of other hematological patients with pancytopenia without radiation exposure. At present, for ARS, cytokines may be administered to appropriately selected victims to mitigate neutropenia in order to reduce their need for subsequent hospitalization and utilization of what will be limited medical resources and personnel. The US/European Consultation Workshop participants felt strongly that both using a particular drug when appropriate and withholding the same when not indicated *were equally important*, and the use of cytokines should be based on clinical information and not given indiscriminately to everyone with potential radiation exposure.

All patients with less than 500 neutrophils per mm^3 are potential candidates for G or GM-CSF. The drug should be initiated as soon as significant hematological injury data are available. Drug should be continued for 14–21 days or until normalization of the granulocyte count. Specific indications for initiating G-CSF therapy include physical dose reconstruction that suggests an exposure of approximately 300 cGy without combined injury or 200 cGy with combined injury. Cytokines should not be used empirically on all patients with radiation exposure.

5. The use of response categories with a severity grading of organ damage to establish the type of medical measures

The medical response that is achievable following a radiation event will be, in large measure, dictated by the size and scope of the event. In general, workshop participants agreed that the goals of care include:

- do no harm
- save lives
- decrease short- and long-term morbidity of survivors
- provide benefit to as many people as possible given the available resources
- deliver of medical countermeasures as quickly as possible for both mitigation and treatment,
- activate and use resources wisely, including, personnel equipment, space and therapeutics; this will require optimized concept of operations
- use effective mitigating strategies, particularly in a mass casualty event, including sheltering-in-place, public messaging, decontamination and appropriate early use of medical countermeasures
- manage psychosocial concerns

There was consensus about different types of “triage” for different scenarios and settings. In a limited radiological event medical personnel would be available for assistance. In a mass casualty setting there would need to be three levels of triage (Chest Suppl May 2008, p 53): an initial rapid triage in the field, secondary triage in the emergency department and a

tertiary triage within the hospital assisted by radiation experts. The primary triage efforts specific for radiation victims is based on environmental physical dosimetry. The goal of the primary triage is to rapidly distinguish three groups of victims: those in the immediate need of medical care (in the order of 4–5 Gy or more), those at risk for the hematopoietic syndrome in the next 1–4 weeks with a dose of 2–4 Gy and those who may need some symptoms management and long-term follow-up but not hematopoietic or clinical treatment. Hospital capacities and facilities must be prepared to accommodate large numbers of patients that require immediate medical care as well as those who will present later with signs and symptoms such as infection and bleeding beyond about 10 days, i.e., those with hematology grades H1 or H2). These later patients show signs and symptoms such as infection and bleeding only beyond about 10 days following exposure.

The METREPOL “clinical triage” assigns a patient to a response category and indicates the severity of effect in the four most important organ systems, such as the neurovascular system, the gastrointestinal system, the cutaneous system as well as the hematopoietic system and leads to therapeutic interventions. This concept is favoured in the USA complemented by the determination of exposure dose by using biodosimetric approaches. The REMM web site [12] provides continual update of radiation medical management knowledge and just-in-time information for medical responders who may not be familiar with the details of ARS. In Europe, Germany for example, when there is a nuclear reactor incident deemed to be a potential public health hazard, pre-determined emergency stations are prepared around the nuclear reactors to screen hundreds of persons, register them and select those persons who need further medical assessment [30].

Additional clinical and laboratory research is needed to develop and validate systems that account for combined multi-organ injuries (i.e. radiation and trauma or burns). Compatible electronic victim tracking tools and electronic health records are essential especially since patients may have to travel to more distant sites for care. Specimen collection and tracking is needed for clinical management, forensics, and research. Guidelines are needed for when to collect what specimen and where to send them for analysis. An increase in laboratory capacity, including mobile laboratories, is absolutely necessary for routine as well as more specialized assays for biodosimetry and radio-bioassay. While the ongoing national planning strategies in the countries of the workshop participants vary from small to large events, planning and concepts of operations developed by the individual countries could be shared among partners, utilizing telecommunication options to bring medical experience to the site of event. Furthermore, guidelines and assistance from national as well as international resources (e.g., IAEA, WHO, Global Health Security Action Group [GHSAG]) will be used when appropriate.

6. Education and training for medical and allied staff

There was a consensus among the workshop participants about the need for appropriate training programs for doctors and allied medical personnel in the field of radiation medical preparedness and assistance that will participate in the actual care of patients. Training programs should be based on mutually compatible concepts and potential medical measures at the international level. The IAEA and WHO have valuable teaching material and guidelines, many of which deal with radiation protection problems as well as rules and regulations regarding radiation accident management.

The concept of some basic education (provided by RITN) with the availability of just-in-time up-to-date information for medical responders (provided by REMM) was favourably received. The workshop participants also recognized that REAC/TS [13] courses have a long history of excellence. Recently an “Advanced Training Course for Physicians” based on the

METREPOL concept [15] has been held as a pilot training event. The course included plenary lectures, and “clinical rounds” to discuss in depth “case histories” from previous radiation accidents. The sessions were extremely productive, since one could ask questions such as “what happened really”, “what measures were taken when” and “what would you have done if such a patient would enter your service”. Workshop participants encourage the publication of the curriculum from this course as widely as possible. The participants also suggested that educational courses offered at a global level would have similar or identical “core topics”. There was a strong support for the idea to have one day for case discussion at a time when the “e-learning part” has been successfully completed. One should furthermore consider “audience specific courses” such as for oncologists and hematologists, dermatologists, surgeons, nuclear medicine, nurses and health physicists. Consideration should be given to the possible integration of radiation curriculum into all-hazard approaches to mass casualty

7. Research and development issues for potential collaborations

The state-of-the-art in radiation injury management is largely based on studies of victims of accidental exposure in small events. Accident registries and clinical course of disease-databases are available at the international level (see Oak Ridge REAC/Ts or SEARCH Database developed in Ulm). Since these represent “rare” diseases of high scientific interest, it is suggested that an international registry of victim clinical histories be created and updated regularly. This would represent an important scientific resource, because it allows study in detail the course of health impairments and the analysis of pathophysiological principles and mechanisms.

In addition, it should be possible to create an international network of laboratories to examine the state of knowledge regarding a number of open scientific questions such as mechanisms of multi-organ response to ionizing radiation (acute as well as chronic) and the pathophysiology of multi-organ failure, which would benefit from the analysis of the clinical observations. Furthermore, new experimental work is needed in the field of therapeutic interventions, including the role of growth factor therapy, stem cell transplantation including mesenchymal stem cells and the self renewal capacities of stem cells of different origin (blood, bone marrow, cord blood, fetal liver) and their interaction with the stem cell niche.

More work is also needed in the field of biodosimetry. It is crucial to come to a consensus regarding the term “dosimetry”. In biological terms, it is well understood that the term “dose” includes cytogenetics, biomarkers, molecular profiling and other methods, some of which depend a great deal on time post exposure, dose-rate and volume of tissue irradiated. It may, however, be very difficult to give a definition of that type of “dose” in comparison to the precision with which a “physical dose” of exposure can be determined. However, in practical terms it will be important to further develop “indicators of effect and repair” as suggested by the National Academy of Sciences (31) and to optimize the interpretation of hematological and cytogenetic indicators. Much of these efforts are on going at the (CMCRs and on an international level.

Finally, it may well be useful to think about a tissue sample repository including the storage of bone marrow and blood cell smears and histological material from radiation accident cases as well as from patients after the use of total or partial body exposure for therapeutic reasons.

8. Overall conclusions and next steps

There was a strong consensus that there are gaps remaining in the knowledge of the mechanisms of the radiation syndromes and the multi-organ involvement that may result in

multi-organ failure. Medical triage will be both symptom-based and dose-based, recognizing that organ dysfunction is related to radiation dose and volume. Furthermore, knowledge from the laboratory and ongoing refinement of the current triage systems will enhance their compatibility and complimentarity. Laboratory and clinical diagnostic assessment tools need to be improved for managing individual victims and for triage. Medical countermeasure use requires ongoing review and updating to optimize patient care so that appropriate measures are used and inappropriate empiric administration of countermeasures is avoided. The development of an effective medical response and the necessary education and training will remain a collaborative work in progress. It is suggested to continue the scientific dialogue between partners such as represented in this workshop

Abbreviations

ARS	Acute Radiation Syndrome
ASBMT	American Society for Blood and Marrow Transplantation - www.asbmt.org/
ASCO	American Society of Clinical Oncology - www.asco.org
ASTRO	American Society for Therapeutic Radiology and Oncology - www.astro.org
CMCR	Center for Medical Countermeasures against Radiation - www3.niaid.nih.gov/topics/radnuc/default.htm
EBMT	European Group for Blood and Marrow Transplantation - www.ebmt.org
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
METREPOL	(**Me**dical **Tre**atment **P**rotoc**ol**s for Radiation Accident)
NAC	Nuclear Accident Committee
NIH	National Institutes of Health
NIAID	National Institute for Allergy and Infectious Disease - www3.niaid.nih.gov
NLM	National Library of Medicine - www.nlm.nih.gov
NMDP	National Marrow Donor Program - www.marrow.org
REACT/S	Radiation Emergency Assistance Center/Training Site - *orise.orau.gov/**reacts***
REMM	Radiation Event Medical Management - www.remm.nlm.gov
RITN	Radiation Injury Treatment Network - www.RITN.org

REFERENCES

1. Bader JL, Nemhauser J, Chang F, et al. Radiation Incident Medical Management (REMM): web site guidance for health care providers. Prehopsital Emergency Care. 2008; 12:1–11.
2. Coleman, CN.; Hrdina, C.; Bader, JL.; Norwood, A.; Hayhurst, R.; Forsha, J.; Yeskey, K.; Knebel, A. Ann Emerg Med. 2008. Medical Response to a Radiological/Nuclear Event: Integrated Plan from the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services. in press

3. Confer, DL. Use of hematopoietic stem cell transplants: cord blood, peripheral blood and bone marrow. Conference on Medical Planning and Care in Radiation Accidents; Oak Ridge. 2003 March 3–7;
4. Dainiak N. Hematologic consequences of exposure to ionizing radiation. Exp Hematol. 2002; 30:513. [PubMed: 12063018]
5. Dainiak, N.; Waselenko, K.; Armitage, JO., et al. Hematology Am Soc Hematol Educ Program. 2003. The haematologist and radiation casualties; p. 473-496.
6. Fliedner TM, Doerr D, Meineke V. Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoietic indicators of effect. Br J Radiol. 2005; (Suppl 27):1–8. 2005. [PubMed: 15673518]
7. Fliedner TM. Nuclear terrorism: the role of hematology in coping with its health consequences. Curr Opin Hematol. 2006; 13:436–444. [PubMed: 17053455]
8. Fliedner TM, Graessle D, Meineke V, Doerr H. Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental whole-body radiation exposure: an essential basis for an evidence-based clinical triage. Exp Hematol. 2007; 35:8–16. [PubMed: 17379081]
9. Fliedner TM, Powles R, Sirohi B, Niederwieser D, on behalf of the European Group for Blood and Marrow Transplantation (EBMT) - Nuclear Accident Committee (NAC). Radiologic and nuclear events: the METREPOL severity of effect grading system. Blood. 2008; 111:5757–5758. [PubMed: 18544701]
10. [Accessed July 5, 2008] Mass Medical Care with Scarce Resources: A Community Guide. Available at: http://www.ahrq.gov/research/mce/mceguide.pdf.
11. Powles R, Apperley J. Major radiation exposure. N Engl J Med. 2002; 347:944–947. [PubMed: 12240687]
12. [Accessed July 1, 2008] Radiation Event Medical Management (REMM). Available at http://www.remm.nlm.gov.
13. REAC/TS web site. Available at: http://orise.orau.gov
14. Fliedner, TM.; Friesecke, I.; Beyrer, K., editors. Medical Management of Radiation Accidents - Manual on the Acute Radiation Syndrome. British Institute of Radiology; London: 2001.
15. Gorin N-C, Fliedner TM, Gourmelon P, Ganser A, Meineke V, Sirohi B, Powles R, Apperley J. Consensus conference on European preparedness for haematological and other medical management of mass radiation accidents. Annals of Hematology. 2006; 85(10):671–679. [PubMed: 16896913]
16. Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med. 2004; 140:1037–51. [PubMed: 15197022]
17. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Rad Res. 1961; 14:213–222.
18. Athens JW, Haub OP, Raab SO, et al. Leukokinetic studies IV: the total blood, circulating and marginal granulocyte pools and granulocyte turnover rates in normal subjects. J Clin Invest. 1961; 50:989–995. [PubMed: 13684958]
19. Fliedner TM, Cronkite EP, Robertson JS. Granulocytopoiesis I. Senescence and random loss of neutrophilic granulocytes in human beings. Blood. 1964; 24:402–414. [PubMed: 14220782]
20. Fliedner TM, Cronkite EP, Killmann SA, Bond VP. Granulocytopoiesis II. Emergence and pattern of labeling of neutrophilic granulocytes in humans. Blood. 1964; 24:683–699. [PubMed: 14235351]
21. Fliedner TM, Graessle D, Meineke V, Doerr H. Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental whole-body radiation exposure: an essential basis for an evidence-based clinical triage. Exp Hematol. 2007; 35:8–16. [PubMed: 17379081]
22. Fliedner TM, Tibken B, Hofer EP, Paul W. Stem cell responses after radiation exposure: a key to the evaluation and prediction of its effects. Health Phys. 1996; 70:787–797. [PubMed: 8635902]

23. Graessle, DH.; Fliedner, TM. Computer assisted severity of effect assessment of hematopoietic cell renewal after radiation exposure based on mathematic models. Conference Proceedings “Biodose 2008”; Hanover, NH, USA. 7–10 September 2008; Health Phys, in press
24. Maekawa, K. Overview of medical care for highly exposed victims in the Tokaimura accident. In: Ricks, RC.; Berger, ME.; O'Hara, FM., editors. The Medical Bases for Radiation-Accident Preparedness: The Clinical Care of Victims. The Parthenon Publishing Group; Boca Raton, FL: 2002. p. 313-318.
25. Gaugler, M-H. A unifying system: does the vascular endothelium have a role to play in multi-organ failure following radiation exposure?. Radiation-Induced Multi-Organ Involvement and Failure: A Challenge for Pathogenetic, Diagnostic and Therapeutic Approaches and Research. In: Fliedner, TM.; Meineke, V., et al., editors. Brit J Radiol Suppl 27. 2005. p. 100-105.
26. Brucer, M. A Medical Report on the Y12 Accident, June 16, 1958. UAEC Report ORINS. 1959. The Acute Radiation Syndrome.
27. Huang S, Ye G, Liang D, et al. The clinical report of 3 cases of subacute radiation sickness (in Chinese). Chinese Journal of Radiation Medicine and Protection. 1989; 9:82–86.
28. Bennett, B.; Repacholi, M.; Carr, Z., editors. Report of the UN Chernobyl Forum Expert Group „Health“, Geneva. World Health Organization; Geneva: 2006. Health Effects of the Chernobyl Accident and Special Healthcare Programmes.
29. Fliedner TM, Tibken B, Hofer EP, Paul W. Stem cell responses after radiation exposure: a key to the evaluation and prediction of its effects. Health Phys. 1996; 70:787–797. [PubMed: 8635902]
30. Strahlenschutzkommission, editor. Veroeffentlichungen der Strahlenschutzkommission - Band 4. Hoffmann-Fachverlag; Berlin: 2007. Medizinische Massnahmen bei Kernkraftwerksunfaellen.
31. Committee on Science and Technology for Countering Terrorism. National Research Council. Making the Nation Safer: The Role of Science and Technology in Countering Terrorism. The National Academies Press; Washington DC: 2002.
32. Calvi LM, Adams GB, Weibrecht KW, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature. 2003; 425:841–846. [PubMed: 14574413]
33. Zhang J, Niu C, Ye L, et al. Identification of the haematopoietic stem cell niche and control of the niche size. Nature. 2003; 425:836–841. [PubMed: 14574412]
34. Arai F, Hirao A, Ohmura M, et al. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell. 2004; 118:149–161. [PubMed: 15260986]
35. Shalaby F, Rossant J, Yamaguchi TP, et al. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. Nature. 1995; 376:62–66. [PubMed: 7596435]
36. Oberlin E, Tavian M, Blazsek I, Peault B. Blood-forming potential of vascular endothelium in the human embryo. Development. 2002; 129:4147–4157. [PubMed: 12163416]
37. Tavian M, Coulombel L, Luton D, Clemente HS, Dieterlen-Lievre F, Peault B. Aorta associated CD34+ hematopoietic cells in the early human embryo. Blood. 1996; 87:67–72. [PubMed: 8547678]
38. Avecilla ST, Hattori K, Heissig B, et al. Chemokine-mediated interaction of hematopoietic progenitors with the bone marrow vascular niche is required for thrombopoiesis. Nat Med. 2004; 10:64–71. [PubMed: 14702636]
39. Kiel MJ, Yilmaz OH, Iwashita T, Yilmaz OH, Terhorst C, Morrison SJ. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. Cell. 2005; 121:1109–1121. [PubMed: 15989959]
40. Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity. 2006; 25:977–988. [PubMed: 17174120]