Note

MEDICAL MANAGEMENT OF RADIATION VICTIMS IN THE UNITED STATES

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Abstract—**Many governmental and non-governmental agencies are involved in the planning for radiation events in the U.S. We will focus on medical management after mass casualty events, specifically the involvement of the Radiation Injury Treatment Network (RITN), a voluntary consortium of medical centers across the continental U.S. RITN and its partners have established standardized approaches for the evaluation and treatment of radiation victims, which are now available online. Efforts are underway to streamline these processes, provide training to healthcare practitioners around the country, and harmonize with similar efforts around the world.**
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INTRODUCTION

EXTENSIVE PLANNING is underway in the United States of America to prepare for accidental and intentional radiation events. These efforts involve local, state and federal government, as well as a variety of non-governmental agencies. Within the federal government, the Department of Health and Human Services, Department of Defense, Department of Energy, Environmental Protection Agency, United States Coast Guard, and Department of Homeland Security are involved in planning for a range of untoward events, from a mass casualty scenario to smaller scale incidents. Other manuscripts in this edition will address specific efforts within the U.S., including the development of medical countermeasures and internal biodosimetry. We will focus on medical management after mass casualty events involving external radiation, specifically the involvement of the Radiation Injury Treatment Network (RITN), a voluntary consortium of medical centers across the continental U.S.

THE RADIATION INJURY TREATMENT NETWORK

Patients exposed to significant doses of total body irradiation invariably develop hematologic toxicity. Thus, hematologists/oncologists are expected to play an important role in the aftermath of radiation events (Weinstock et al. 2008). Recognizing this, the U.S. National Marrow Donor Program (NMDP) first established a relationship with the U.S. Navy in 1986 to explore a role for the NMDP in planning and response efforts. After the attacks on 11 September 2001, the NMDP began developing a core network of U.S. medical facilities to provide intensive management for radiation victims. The American Society for Blood and Marrow Transplantation (ASBMT) joined the effort and, in 2006, the initial network of 13 centers was established. That network, now known as RITN, comprises 57 hematopoietic stem cell transplant (HSCT) centers, stem cell donor centers and umbilical cord blood banks (Fig. 1). RITN depends on cooperative partnerships with both governmental and nongovernmental agencies, including the Office of Naval Research, the Center for International Blood and Marrow Transplant Research, and the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services.

More information on RITN efforts, educational resources, standardized treatment approaches, a medical grand rounds presentation, and Web links are available at http://www.nmdp.org/RITN/index.html. Briefly, the goals of RITN are (1) to develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure, (2) to educate health care professionals about pertinent aspects of radiation exposure management, (3) to assist with coordinating the medical situation response after a radiation event, and (4) to provide comprehensive evaluation and treatment for victims at

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Fig. 1. RITN network.

participating HSCT centers. It should be noted that RITN members are not first responders or decontamination specialists, but experts in the management of patients with hematologic injury.

UNIQUE ASPECTS OF EVENT PREPARATION

Harmonization between efforts in the U.S. and other countries can only foster improvements in the preparation for and response to radiation events, whether by an individual nation or collectively with regional and distant partners. However, clear differences exist between the medical management approaches developed by RITN and those developed within the European Community (EC) (Fliedner 2006; Gorin et al. 2006). These differences primarily relate to two issues. First, the predominant focus of RITN is on preparation for and response to a *mass casualty* event, such as an improvised nuclear device. In contrast, planning efforts in the EC have primarily addressed scenarios affecting, at most, a few thousand persons. The importance of this distinction cannot be overstated. Efforts to manage relatively small numbers of patients can and should build primarily on previous experience with radiation accident victims. In contrast, the logistical complexity of patient management after a mass casualty radiation event is unprecedented and presents completely different challenges.

It is simply not possible to be completely prepared for a mass casualty event that affects hundreds of thousands or millions of people. Instead, each country or network of countries can only realistically undertake the preparations that are possible within their resource constraints. Thus, the second primary difference in planning between the U.S. and EC is the nature of resources dedicated to responding to these events. For example, the availability of geographic dosimetry around major population centers in the U.S. will allow for out-of-hospital triage of large numbers of people within a certain radius. A second example is the U.S. Strategic National Stockpile, which includes medication that could be dispensed to myriads of victims within 24–48 h after a mass casualty event.

With these differences in mind, harmonization to whatever extent possible remains mutually beneficial, as unique expertise, resources, and abilities exist within all regions of the globe. The initial effort to harmonize approaches, a consensus meeting between representatives from the U.S. and EC that was held in Ulm, Germany in July 2008, is described elsewhere in this edition.

PREDICTING THE CLINICAL EFFECTS OF RADIATION EXPOSURE

A document on extensive planning for the response to a mass casualty radiation event, including field triage,

was published by the Office of the Assistant Secretary for Preparedness and Response (Coleman et al. 2009). According to current models, the appropriate selection of patients for referral to treatment centers or pre-emptive administration of growth factors (e.g., G-CSF) will require practitioners in the field to estimate an individual patient's likelihood of developing clinically-meaningful sequelae of radiation exposure. Current efforts in the U.S. to stratify victims based on risk for clinical complications are primarily focused on estimates of radiation dose. Beside geographic dosimetry, plans have been formulated to develop major radiation laboratory networks to perform dicentric quantification on a mass scale (Dainiak et al. 2007). In addition, newer methods for biologic dosimetry, including rapid genomic analysis, serum proteomics, and measurements of DNA damage, are under development.

Upon referral to specialty centers, treating hematologists may need to calculate radiation doses using whatever information they have available. Online algorithms for estimating a victim's dose based on clinical and biological data are available from the Radiation Event Medical Management (REMM) Web site (Bader et al. 2008) at http://www.remm.nlm.gov/ars_wbd.htm or from the Armed Forces Radiobiology Research Institute at http://www.afrri.usuhs.mil/outreach/biodostools.htm. The METREPOL (MEdical TReatment ProtocOLs for radiation accident) strategy (Friesecke et al. 2001) developed in the EC is also available on the REMM Web site and may be highly useful for patients at centers where (1) adequate laboratory and clinical facilities are available and (2) hematologic measurements are not confounded by the early administration of growth factors.

STANDARDIZING MEDICAL RESPONSE IN THE U.S.

Persons exposed to radioactive material will present unique and exceedingly complex management challenges. Few physicians are familiar with the basic manifestations of acute radiation injury or have training in the prospective management of patients with significant radiation exposure. Thus, easily-accessible and widely-available treatment guidelines for the management of radiation victims are essential. The Radiation Event Medical Management Web site (http://www.remm.nlm.gov), developed through a collaboration between the National Library of Medicine, Office of the Assistant Secretary for Preparedness and Response, and medical experts from around the world (Bader et al. 2008), includes admission and treatment order templates directed toward victims of radiological or nuclear events.

Although REMM contains recommendations for many aspects of radiation victim management, several issues remain. Nearly all of the recommended approaches are based on either anecdotes, experimental findings in animal models, or extrapolation from other patient populations, such as those treated with myelosuppressive chemotherapy. In addition, many questions have not been addressed. For example, will patients who recover after high doses of radiation require long-term antimicrobial prophylaxis or revaccination? Alternatively, what dose of total body irradiation is invariably lethal? Addressing such questions through international collaboration remains a high priority.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Perhaps the most contentious issue in the medical management of radiation victims revolves around the role of allogeneic HSCT. Some victims of a large-scale event may receive sufficient doses of radiation to cause either irreversible myeloablation or myelosuppression lasting longer than the patient can survive. These patients will commonly have concurrent damage to other organ systems, which is known to markedly reduce survival in irradiated nonhuman primates. Thus far, 31 patients who received allografts after radiation accidents have been reported in the literature (Dainiak and Ricks 2005). A variety of pre-transplant conditioning and post-transplant prophylaxis regimens were used in these patients. The outcomes have been abysmal, with none of the 31 patients obtaining persistent engraftment and survival for longer than one year. Severe graft-vs.-host disease (GVHD) was also common, arguing that patients who might otherwise reconstitute autologous hematopoiesis may actually be harmed by the transplant (Dainiak and Ricks 2005). Thus, it remains unclear whether allogeneic HSCT can be a life-sustaining measure in this setting.

In the early days following a mass casualty event, however, it is likely that large numbers of victims with cytopenias and no physical injury will appear to be potential allogeneic HSCT candidates. The NMDP and RITN have established recommended approaches for Human Leukocyte Antigen (HLA)-typing and pre-transplant conditioning, respectively. NMDP has anticipated the need to conduct large numbers of urgent donor searches for victims following a large-scale event, recognizing that only a few searches would likely lead to actual transplants. Buccal swabs can be used to obtain DNA for HLA-typing, as victims who have received high doses of radiation may not have adequate numbers of peripheral blood mononuclear cells to perform typing.

NMDP-contracted HLA-typing laboratories currently perform 5,000–6,000 HLA typings weekly and would be used to HLA-type victims in need of urgent donor searches. NMDP's Internet-based computer systems acquire HLA-typing data directly from the laboratories and make it available for automated matching of adult donors and cord blood units to potential transplant recipients. The computer systems also facilitate contact and communication with the adult donors, whose HSCT donations must be scheduled, and with cord blood banks. Around-the-clock availability of the NMDP computer systems has been established to facilitate the extended operating hours necessary to manage an increased search load.

For an individual radiation victim, the consideration of prompt HLA-typing and rapid donor identification will depend on evidence that suggests prolonged and possibly irreversible myelosuppression. This evidence could include an estimated whole body exposure of greater than 4 Gy, or clinical indicators such as hyperacute vomiting or the rapid onset of cytopenias. Concomitant burns, injuries or organ dysfunction should be considered as contraindications to HSCT, as they would be for other HSCT candidates.

The RITN regimen for pre-transplant conditioning is similar to an approach tested in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN Protocol 0301) for the treatment of aplastic anemia (http://spitfire.emmes.com/study/bmt). Similar to patients with aplastic anemia, radiation victims considered for HSCT will already be neutropenic from radiation exposure. Thus, pre-HSCT conditioning will require sufficient immunosuppression to ensure engraftment but not myeloablation. The modified regimen includes cyclophosphamide, anti-thymocyte globulin, and fludarabine. GVHD prophylaxis includes cyclosporine (or tacrolimus) and mycophenolate. Based on previous experience, this approach is suitable for matched related, unrelated, or cord blood donors (Brunstein et al. 2007). The use of a standardized regimen will allow for post-event analysis and refinement of the approach. Elements of the RITN regimen, including donor matching and selection and necessary supportive care, are outlined at http://www.nmdp.org/RITN/index.html.

DATA COLLECTION AND COMMUNICATION

The experiences from Japan and Chernobyl clearly indicate that the long-term complications from a mass casualty radiation event, both medical and psychological, will be extensive. To ensure optimal long-term care and enhance preparedness for subsequent events, the NMDP has developed a data collection protocol for all radiation victims managed at RITN centers. The data collection protocol is available online (http://www.nmdp.org/RITN/GUIDELINES/DOCS/data_collection_prot.pdf) to facilitate use by clinicians who are managing victims at non-RITN centers. RITN centers will contribute patient data to central repositories, either through RITN or governmental agencies. Optimally, these data will be entered in real-time, so that recommendations can be rapidly modified as data become available. However, this data set is likely to include only a small fraction of all radiation victims after a mass casualty event. Thus, extensive field-based epidemiology and follow-up surveillance by local and federal authorities will be essential.

In addition, RITN teleconferences are held regularly to address ongoing issues at participating centers. Each RITN center was also issued priority telecommunication equipment to ensure that centers remain in contact in the aftermath of an event.

EDUCATION AND TRAINING

RITN has taken multiple approaches to improve education and training among healthcare workers at RITN and other centers. In September 2007, RITN convened a one day meeting in Bethesda, Maryland, entitled "Medical and Organizational Challenges Resulting from a Radiological or Nuclear Emergency" that addressed both progress and outstanding issues in the response to radiation events. A similar meeting was held in Washington, DC, in May 2009.

In addition, basic radiation training is available through the RITN Web site (http://www.nmdp.org/RITN/index.html) and has been completed by over 1,600 healthcare professionals at RITN centers. RITN members also participate in annual tabletop exercises and can undertake additional training through collaboration with the Radiation Emergency Assistance Center/Training Site (*REAC/TS*).

CONCLUSION

Many governmental and non-governmental agencies are involved in the planning for radiation events in the U.S. Standardized approaches for the evaluation and treatment of radiation victims are now available online. Efforts are underway to streamline these processes, provide training to healthcare practitioners around the country, and harmonize with similar efforts around the world.

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