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Stem cell transplantation - Section 17

Medical management of acute responses to radiation

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Take home messages

- Preparedness for possible nuclear terrorism is important and possible.
- Multiple parts for preparedness are in place.

Introduction

People exposed to high levels of radiation (usually >1–2 Gy over a short period of time may develop acute radiation syndrome (ARS). Symptoms vary according to the dose but include vomiting, diarrhea, headache, dizziness, weakness, bleeding, and redness of the skin. In a large mass casualty setting, efficient triage of irradiated casualties is essential to identify those who have received clinically significant but not invariably lethal doses of radiation estimated at 2-Gy of whole body exposure. These are the victims that need specialized and sometimes urgent care. In resource scarce settings, symptomatic care is given if possible and life-sustaining measures should be withheld from casualties with non-survivable trauma, thermal burns and/or radiation exposures. Extensive triage algorithms that emphasize fairness were recently published to guide the selection of appropriate candidates for life-sustaining care in resource- limited settings in order to maximize survivability for the overall population.[1]

Current state of the art

The current management of ARS does not substantially differ from the management of pancytopenia in other settings, such as after treatment with myelosuppressive chemotherapy. Recently (2015), the FDA approved the use of Neupogen, Neulasta and Leukine for the treatment of hematopoietic ARS, administering myeloid cytokines to appropriately select victims offers 2 potential benefits after a mass casualty radiation incident. It can reduce morbidity and mortality resulting from neutropenia and it can lessen the need for subsequent or continued hospitalization during the post-incident period when medical resources and personnel may be extremely limited. The current challenge is that the local supply of cytokines would be quickly depleted in the absence of adequate triage to ensure that those that may not require this treatment immediately are referred for later evaluation and possibly treatment in a more resource-rich environment. Examples of activities in resource limited settings would include victims treated in a gymnasium or school or reducing the dose of growth factors.

All patients with confirmed neutropenia or medical history of radiation exposure and physical injuries strongly suggestive of combined injury (radiation *plus* trauma and/or burn) are potential candidates for myeloid cytokines if they are deemed to have survivable exposure/injuries. Studies in non-human primates suggest that *initiating myeloid cytokines within* 24 *hours of exposure* may improve outcomes.*[2] Myeloid cytokines (granulocyte-colony stimulating factor (G-CSF; Filgrastim), granulocyte monocyte-colony stimulating factor (GM-CSF; sargramostim) or pegylated G-CSF (pegfilgrastim)] can reduce the duration of neutropenia, hospital length-of-stay, and overall costs.

Myeloid cytokines should be initiated as soon as there is evidence a casualty will develop severe neutropenia (ie, less than 500 neutrophils per mm3). Specific indications for initiating myeloid cytokines prior to the onset of neutropenia include a projected whole body dose of 2 Gy or more based on (1) physical dose reconstruction using geographic information, (2) clinical signs, and/or (3) lymphocyte depletion kinetics. Drugs should be continued until normalization of the granulocyte count. Supportive care measures are equally important. Antiemetics for vomiting, hydration, and antibiotics to prevent bacterial infections during the neutropenic period have been shown to improve survival in animal models of ARS. These suggestions are not different from those that are in daily practice in the heme-onc or transplant wards.

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Table 1

The Spectrum of Potential Events Involving Radioactive Material. Numbers of Deaths are Rough Estimates.

Categories	Description	Number of Deaths
Radioactive source accident	Loss or theft of a radiological source (eg, Goiana, Thailand, Mexico)	0–10 s
Nuclear reactor accident	Release of radioactive gas or material (eg, Chernobyl, Mayak)	0–100 s
Radiological dispersal device	Device or scheme for dispersing radioactive isotope (eg, dirty bomb* or radioactive material in the food supply)	0–1000 s
Radiological exposure device	Radioactive material intended to expose people in the vicinity (eg, Cesium source placed on a train, China)	0–100 s
Improvised nuclear device	Incorporates radioactive material intended to produce a nuclear explosion	1,000s to >1,000,000

* Only a small fraction of deaths would be expected to result directly from radiation exposure.

The essential role of biodosimetry

Appropriate triage and care after radiation exposure depends on accurate and timely estimates of radiation dose. Dose information will be important for classifying victims into groups that: (1) will not require medical intervention, (2) could benefit from supportive care (eg, colony stimulating factors) to facilitate autologous marrow recovery, (3) require evaluation for HSCT to treat potentially irreversible marrow damage, and (4) cannot be salvaged. A variety of information can be used to estimate an individual's radiation exposure. Unlike the homogenous dosing associated with therapeutic total body irradiation, shielding from nearby structures (eg, buildings) during accidents or terrorist attacks will result in heterogeneous exposures. Therefore, a careful history of the victim's location and subsequent symptoms will be essential. Initial clinical assessment will include the time from event to first emesis and peripheral blood counts, with subsequent lymphocyte depletion kinetics.

Approaches that use only clinical and routine laboratory findings to stratify victims into risk groups are valuable for a small-sized accident, but their utility during large events is not clear.[3,*4,5] Biodosimetry, the use of biologic markers to assess dose, can enhance the predictive value of clinical findings after radiological or nuclear events. The "gold standard" for biodosimetry is the quantification of dicentric chromosomes using metaphase cytogenetics in peripheral blood lymphocytes. Unfortunately, dicentric quantification requires multiple days to perform and is currently available only in selected centers. Plans have been formulated to develop major radiation laboratory networks to perform dicentric quantification on a mass scale.[6] Newer methods for biologic dosimetry, including rapid genomic analysis of PBLs, serum proteomics and measurements of DNA damage, are also under development.[*7,8,9]

Treating hematologists will need to calculate radiation doses using the information they have available. Online algorithms for estimating dose based on clinical and biological data are available from the Radiation Emergency Medical Management (REMM) website at http://www.remm.nlm.gov/ars_wbd.htm or from the Armed Forces Radiobiologic Research Institute at http://www.afrri.usuhs.mil/www/outreach/biodostools.htm#software.

Future perspectives

A role for stem cell transplantation?

Some victims of a large-scale event may receive doses of radiation to cause irreversible myeloablation. As discussed above, these patients will commonly have multi-organ damage.

What remains unclear is whether allogeneic HCT can be a life-sustaining measure in this setting. To date, 31 patients have undergone allogeneic HCT after accidental radiation exposure. Median survival after transplant for these patients is ~1 month.[*10] All 4 patients who survived >1 year reconstituted autologous hematopoiesis, raising the question whether the HCT provided any benefit. Particularly troubling was the contribution of GVHD to mortality in >20% of patients. More recently previously unavailable data on the use of stem cell administration to aid recovery of victims of the Chernobyl disaster became available.[*11] There were 9 patients heretofore unreported in the scientific literature who underwent intraosseous injections of allogeneic bone marrow cells in Kyiv. Transplantation was associated with significantly shortened time to recovery of granulocyte and platelet counts in these patients.

While current guidelines would certainly include the use of cytokines, these data provide an indication of the effectiveness of stem cell transplant to treat victims of radiation exposure.

In many regards, patients with myeloablation from radiation exposure are similar to those with aplastic anemia. A reduced intensity conditioning regimen for severe aplastic anemia (where immunosuppression but not myeloablation is required) is being tested in the Blood and Marrow

Transplant Clinical Trials Network (BMT CTN Protocol 0301).[12] Of note, NMDP has plans in place to conduct large numbers of urgent searches for victims following an event, recognizing that only a few searches would likely lead to transplants (Table 1).

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