

Radiation Emergencies: Evaluation, Management, and Transplantation

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ABSTRACT

Radiation or marrow toxic emergencies can lead to severe pancytopenia along with other multiorgan injury. Experience in managing severe myelosuppression suggests that hematology, oncology and transplantation physicians should participate in preparedness planning for such events. Evaluation and management of marrow injured patients requires their expertise. Understanding of the biology of radiation injury, clinical dosimetry to estimate exposure and defined elements of supportive care are essential for appropriate emergency and follow-up treatment. Some patients with expected radiation exposure >4Gy may have extended myelosuppression and be candidates for consideration of allogeneic hematopoietic stem cell transplantation (HSCT). Issues related to patient screening, supportive care, and planning for transplantation are best addressed ahead of time to enable readily available information and guidelines for patient management. National and international contingency planning for such urgencies is underway as effective emergency mobilization requires forethought, education, and pre-established protocols for treatment. Radiation and marrow toxic emergencies may seem unlikely, but the best approach to appropriate medical support is preparedness, contingency planning, and planned research to improve guidelines for the future.

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KEY WORDS

Radiation • Contingency planning • Stem cell transplantation

INTRODUCTION

Accidental exposure to myelotoxic radiation or chemicals in a terrorist, industrial accident, or military circumstance is a current and continuing threat. Sudden high-dose exposure from a blast or radiation leak or slow ongoing partial body exposure from a dirty bomb or radiation dispersal device left in a public place may produce differing exposure and intensity. Appropriate management of the hematologic consequences and the injury, trauma, or burns requires planning and preparedness for contingencies [1-4]. Beyond the first response of assessment, stabilization of trauma, and treatment of burns, evaluation and management of myelosuppression create clinical circumstances most familiar to physicians managing pa-

tients with hematologic cancer or HSCT [1,2,5]. Pancytopenia and immune suppression are also consequences of acute radiation syndrome [6,7]. Appropriate contingency planning allows foresight and preparedness to develop evaluation and treatment guidelines [8]. Experience from previous radiation accidents has spurred planning in the United States and in Europe. Some experiences in responding to urgent mass medical contingencies (eg, hurricanes) can inform plans for management of radiation emergencies.

HSCT FOR TREATMENT OF RADIATION-INDUCED MYELOSUPPRESSION

Published experience documents >30 patients undergoing HSCT for treatment of irradiation-associ-

ated marrow toxicity [1,3-5]. Only 4 patients survived and all rejected their graft, thus emphasizing the complexities in assessing extent of immune suppression which might be distinct from myelosuppression. Identifying proper and expediently available donors, conditioning regimen, GVHD prophylaxis, plus supportive care techniques tailored to the irradiated patient are challenging. These may differ from the preplanned, defined exposures accompanying conventional HSCT for treatment of cancer or other life-threatening diseases. Some published experience has included serial transplantations of grafts from numerous donors because of graft failure [3,9,10]. This highlights the difficulty in assessing the extent of immunosuppression experienced by patients undergoing intermediate-dose, whole or partial body irradiation. In general, patients exposed to 4-9 Gy will develop significant myelosuppression. However, at the lower end of this dose range (2-4 Gy), hematologic recovery without stem cell support might be expected. Above these limits additional multiorgan toxicity from acute radiation syndrome might limit survival. Trauma, burn or infection greatly complicates these assessments because animal models and clinical experience suggest that multiorgan injury in addition to radiation-associated myelosuppression greatly augments mortality and might lower the dosimetry-based indications for stem cell support to achieve prompt and survivable hematologic recovery.

Recommendations published by the US Strategic National Stockpile Working Group support the concept of a limited dose range for which transplantation should be considered as therapeutically appropriate, particularly when a large number of victims is involved [2,9,10]. Limited exposure yielding only a few victims could broaden the threshold for intensive transplantation support without overtaxing available resources. Several recent reviews have outlined management considerations for radiation accidents and emphasized this decision making in detail [2,4,9,10].

BIODOSIMETRY

Clinical assessments of radiation exposure using simply available bedside and laboratory observations are imprecise but are generally agreed to be the most reliable and available tools to determine who might need and/or benefit from allogeneic HSCT in addition to other supportive care [2,7,11,12]. These biodosimetry tools are generally applicable to high-dose uniform exposure. Importantly, they are less applicable and less reliable for nonuniform radiation exposure that might spare substantive areas of BM and still be permissive of at least partial hematologic recovery without transplantation. Tools to estimate biodosimetry are available (www.affri.usuhs.mil). Time to vomiting from initial exposure is a generally accepted measurement of whole body dosing. Significant vom-

iting within 1-2 h likely implies whole body radiation dosing >4 Gy, but is neither specific to radiation nor always seen with high-dose exposure. The rate of development of lymphocytopenia and granulocytopenia is readily measurable. In the absence of research-level studies, evaluating chromosomal breakage and other techniques are not generally available. Lymphopenia (lymphocyte count <1000/ μ L) within 5-7 days or absolute neutropenia (neutrophil count <1000/ μ L) anytime within 2 weeks implies widespread marrow suppression which is expected from >4Gy. This presentation should suggest that consideration and planning for HSCT might be appropriate.

EARLY EVALUATION FOR HSCT

Initial patient/radiation victim evaluation should include date and time assessments of the circumstances of the radiation exposure, details of physical examination, and basic laboratory data including complete blood cell count and differential. Outline of pre-existing medical conditions and comorbid burns, trauma, or infections are important components of patient assessment, triage, and planning for support. Partial or whole body exposure to substantive doses of radiation includes toxicity to hematopoietic, gastrointestinal, and cerebrovascular systems, with particular toxicity to rapid cell turnover in lymphopoietic, epithelial, and epidermal tissues [2,3,7].

SUPPORTIVE CARE

First responders encounter potential radiation victims and should recognize that early initiation of filgrastim (5-10 μ g/kg per day) and oral dosing with potassium iodide (130 mg/day for adults) is indicated. Patients showing signs of >3-Gy whole body estimated exposure (2 Gy for children and the elderly) have a need for intensive management and early filgrastim support. Late administration of growth factors may be ineffective [2,4,8,13-15]. Transfusion support with red blood cells and platelets are indicated. Blood products should be irradiated to prevent transfusion associated GVHD because the extent of immunosuppression cannot be reliably assessed. Transfusion-associated GVHD may overlap with and resemble radiation exposure because its symptomology includes fever, rash, diarrhea, and pancytopenia. Prophylactic antibiotics directed toward gram-negative bacilli using extended-spectrum quinolones or similar agents and suppression of yeast colonization with fluconazole or alternative agents may also be indicated as detailed in the recommendations for management of patients with therapy-associated neutropenia published by the Infectious Diseases Society of America and the American Society for Blood and Marrow Transplantation [16,17].

DONOR SEARCHING

Patients whose initial biodosimetry assessments (time to vomiting and leukopenia measurements), identified above, and quantified using the public software available can identify patients for whom allogeneic HSCT might be indicated. This also indicates the need for urgent donor searching. For any patients requiring possible allogeneic transplantation, rapid collection of buccal swab and blood samples from the patient and immediate siblings are indicated to determine availability of a related allogeneic donor. High-resolution, allele-level HLA typing for HLA-A, -B, -C, and -DR loci should be performed on the potential recipient to facilitate rapid identification of an allogeneic unrelated volunteer or cord blood donor in case no family donor is identified.

INDICATIONS AND TECHNIQUES FOR HSCT

For patients with prolonged pancytopenia (no recovery within 21-28 days) or those whose immediate estimated whole body exposure is $>4-6$ Gy, allogeneic HSCT will be required to promote hematologic recovery and survival [2,4,8,9]. Because irradiation victims may be significantly myelosuppressed, but inadequately or incompletely immunosuppressed, they may require additional immunosuppression to facilitate allogeneic hematopoietic cell engraftment, particularly from unrelated or partially matched donors. Because marrow failure is their primary defect, the irradiation victim's clinical syndrome resembles transplantation for aplastic anemia in the conventional therapeutic setting. In addition, because pre-existing radiation exposure and injury may reduce their tolerance for intense pretransplantation conditioning, reduced intensity immunosuppressive but nonmyeloablative conditioning may be most appropriate. Transplantation models for irradiation victims may therefore resemble the widespread recent use of nonablative conditioning to sufficiently immunosuppress the recipient to prevent graft rejection without added multiorgan or epithelial toxicity. Although low-dose total body radiation has been widely applied for nonmyeloablative transplantation, it seems intrinsically less appealing to apply to the radiation victim. It may further compound epithelial or other injury induced by the accidental radiation. Before HSCT, highly immunosuppressive pharmaceuticals including fludarabine, alemtuzumab, or ATG might be employed, perhaps accompanied by single-dose cyclophosphamide, the most immunosuppressive of the commonly used alkylators. Similarly, GVHD prophylaxis without epithelial toxicity (avoiding methotrexate) is indicated. Using cyclosporine or tacrolimus in addition to mycophenolate mofetil can augment immunosuppression to prevent rejection and prevent GVHD.

Supportive care through the transplantation procedure should resemble conventional reduced intensity transplant approaches with irradiated transfusion support, filgrastim to accelerate myelopoiesis, and prophylactic and aggressive use of empiric and therapeutic antibiotics.

LOGISTICS OF CONTINGENCY PLANNING FOR MYELOSUPPRESSION AFTER IRRADIATION

Planning for management of radiation victims is intimidating but essential. It forces hematologists, oncologists, and transplantation experts to consider the frightening scenarios of nuclear device explosions, mass casualties, and public health chaos, circumstances that are foreign to transplantation experts. Published model estimates of victims suggest that a 1-kiloton improvised nuclear device in major city could expose up to 33 000 patients to 3-5 Gy of radiation requiring critical support and 19 000 more to 5-8 Gy, likely requiring transplantation [2,4,8]. These demands are well beyond any possible capacity to even contemplate urgent and intensive hematologic and transplantation care with the necessities of antibiotics, blood products, transplantation beds, and transplantation physician expertise. Greater exposure (a 10-kiloton explosive) would markedly increase the number of traumatic injuries and increase the number of victims with life-threatening hematologic toxicity by 3- to 5-fold. Limited victim radiation accidents and industrial or contained military or terrorist exposure could yield only a few or even hundreds of patients requiring support and care at centers remote from the site of initial injury and radiation exposure where the medical infrastructure is undamaged. Effective management of patients, even after transport, cannot take place without contingency planning, preparedness, and pre-established therapeutic protocols for evaluation, management, and treatment.

Additional elements required for effective preparedness are prospective data collection to learn from each experience and to improve processes and techniques for the next events. Satisfactory contingency protocols, resembling prospective phase II trials, must be reviewed and established across a preparedness network to allow prompt activation and treatment. Similarly, their review and acceptance by donor and cord blood networks to provide unrelated hematopoietic cell donors for those in need must be preplanned and designed for urgent activation and action.

SUMMARY

Foresight, planning, and education are not always sufficient to manage medical urgencies, particularly when facing frightening and uncertain experience or

too many urgent victims. The challenge to the hematology, oncology, and transplantation community is to think ahead, to plan, and be prepared. Developed expertise to support elective transplantation for cancer could be life-saving for radiation accident victims of the future. Contingency planning will help us manage this challenge, even while we hope it never occurs.

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