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Acute Radiation Injury: Contingency Planning for Triage, Supportive Care, and Transplantation

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ABSTRACT

Evaluation and management of victims of exposure to myelosuppressive radiation in a military, terrorist, or accidental event is challenging. The hematopoietic syndrome with marrow suppression and pancytopenia follows intermediate intensity radiation exposure and as such produces a clinical syndrome similar to that after myelosuppressive chemotherapy or stem cell transplantation. Therefore, hematologists, oncologists, and transplantation physicians have the opportunity and challenge to plan for care of irradiation victims. Management of the hematopoietic syndrome, as a component of acute radiation sickness, requires understanding its manifestations and implementation of clinical biodosimetry to provide appropriate therapeutic support. Hematopoietic growth factors may be of value if administered early as a component of supportive care. Planning for urgent stem cell transplantation for those with intermediate- to high-dose radiation (4-10 Gy) may be required. Establishing contingency plans for triage, assessment, supportive care, and treatment resembles the development of phase II trials, with defined eligibilities, treatment plans, and incorporated data collection to assess results and plan further improvements in care. The hematology/oncology community is most suited to participate in such contingency planning, and the necessary elements for its success are reviewed.

KEY WORDS

Radiation injury • Contingency planning • Transplantation

INTRODUCTION

The potential risk of accidental and intentional radiation exposure is growing. The dangers are understated and potentially devastating. This requires medical contingency planning and preparedness. Such planning should include an examination of our current resources, projected medical needs, management guidelines, and personnel training. Exposure to whole-body irradiation can induce pancytopenia and immune suppression consequent to the acute radiation syndrome in addition to burns, multiorgan injury, and trauma. Analysis of techniques and experience gained from hematopoietic cell transplantation (HCT) may aid preparedness planning to develop management guidelines. In this report we describe scenarios and medical consequences of radiation, previous HCT attempts, and the potential of cytokines to help. We also discuss how the design and development of clinical trials can resemble contingency planning and inform clinical management of radiation emergencies.

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STEM CELL TRANSPLANTATION FOR ACCIDENTAL OR DELIBERATE NUCLEAR EXPOSURE

Stem cell transplantation has been performed for patients with malignant diseases for >50 years. A recent review of transplantation for irradiation victims assessed 31 patients who underwent HCT from a variety of cell sources [1]. Among these, 27 died and 4

survived after rejecting their graft. Most of these patients were treated in an earlier era but these data have engendered a sense that there is only a limited role for allogeneic HCT in victims of radiation injury. The more recent data from the Tokaimura accident, where 1 patient received a peripheral stem cell transplant and another a cord blood transplant, suggest that, although engraftment of the donor cells was transient, the overall survival in these patients was longer than expected from the radiation dose and organ toxicity [1,2]. Recently, recommendations have been drafted by the US Strategic National Stockpile Working Group that propose a limited dose range for which transplantation should be considered a therapeutic option for victims in a large-volume scenario [3]. The limited success of a fully ablative allogeneic HCT includes the damage to other organ systems such as the lungs, the gastrointestinal tract, and the immune system. It should be emphasized that the value of autologous or allogeneic HCT for radiation victims is largely anecdotal and effective contingency planning requires critical analysis of the results.

A more detailed review of one modern day HCT is illustrative of what can be accomplished and highlights the need for further research in this area [2]. One important caveat in planning support for radiation victims is the potential for high-dose but nonuniform irradiation to organs and tissues, making the estimate of the irradiation dose difficult. Accordingly, estimates of marrow and stem cell irradiation are imprecise, which complicates the prediction of autologous recovery. One victim received 8 to 10 Gy of equivalent mixed neutron and γ-ray irradiation at the JCO Co. Ltd. nuclear processing facility in Tokaimura, Japan. This patient received an HLA-DRB1, mismatched, unrelated umbilical cord blood transplant. Donor/recipient mixed chimerism was attained. Subsequently, immunosuppressive drugs were discontinued and the patient experienced rapid autologous hematopoietic recovery but had persisting and profound immune deficiency. There were increases in naive T cells and helper T-cell subtype 1, but the mitogenic responses of T cells and the allogeneic mixed leukocyte reaction were severely suppressed. Endogenous immunoglobulin production remained low until 120 days after the accident. Ultimately, the patient died of infection and acute respiratory distress syndrome 210 days after the accident.

These results suggest that the use of donor cells was sufficient for survival from the acute hematopoietic syndrome associated with these higher doses of radiation (Figure 1). Therefore, the immediate needs of such patients (recovery of myelopoiesis) were supported by the transient engraftment of donor cells, although the exact benefits provided by the multiple therapies provided are uncertain. Injury to other organs such as the skin (burns, trauma), the lungs (interstitial pneumonitis), or the immune system are an added hurdle in their management, as was recognized in managing the victims of Chernobyl [4].

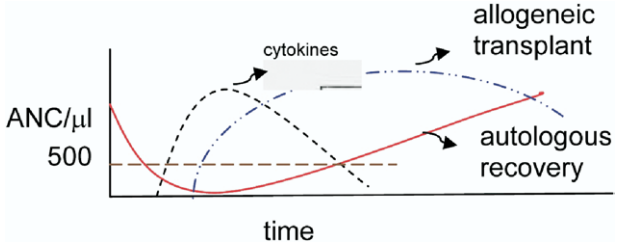

Figure 1. Hypothetical blood count recovery based on allogeneic HCT (dashed/dotted line) or autologous recovery after lesser exposure (solid line), perhaps supported by early cytokine therapy. ANC, absolute neutrophil count.

Since the Tokaimura accident, the HCT procedure has also evolved with significant improvements in supportive care, newer sources of stem cells and improved immunosuppressive drug regimens. An alternative strategy for victims of radiation injury may be the use of a decreased intensity, nonmyeloablative HCT. The immune system of the recipient is targeted, with only limited toxicity to myeloid cells. Because the hematopoietic syndrome is one of the most important sequelae from radiation exposure, it is imperative that options to address the rescue of bone marrow are pursued. It is possible to treat radiation victims by using protocols developed for patients with malignancy. The hypothetical scenario demonstrated in Figure 1 leaves several possible outcomes for a recipient of a deterministic dose of irradiation (2-10 Gy, without significant other-organ toxicity). The victims' blood counts will decrease predictably according to the radiation dose received. For relatively low doses (2-4 Gy), endogenous recovery of autologous hematopoiesis is expected, perhaps enhanced by early cytokine therapy (see below). Victims receiving higher doses (6-10 Gy) may require allogeneic or, if available, cryopreserved autologous hematopoietic cell support. Although it is comfortable to think about dose as a method to determine the necessary course of action, important limitations of radiation dosimetry must be considered, especially in the case of a mass casualty scenario. First, the dose of radiation is not likely to be reliably estimated due to nonuniform exposure (therefore possibly sparing areas of bone marrow). Second, there are no rapid methods to determine the absorbed dose in an individual patient. Time to vomiting [5] is advocated but is neither specific to radiation nor always seen with significant exposure. Therefore, the rate of decrease in blood counts (lymphocytes, granulocytes, and platelets) is likely to be the most useful method that is currently available for rapid decision-making [3,5]. The presence and frequency of chromosomal aberration may be reliable, but it is not widely

Table 1. *Mass Casualty Scenario for an Improvised Nuclear Device**

Patient Category	Radiation Dose, Gy	Patients, n	
		1 Kiloton	10 Kiloton
Combined injuries	**All doses**	**1000-3000**	**15 000-24 000**
Fallout			
Expectant/palliative	**8.3-15**	**18 000**	**45 000**
Intensive care	**5.3-8.3**	**19 500**	**79 400**
Critical care	**3-5.3**	**33 000**	**108 900**
Normal care	**1.5-3**	**66 000**	**70 000**
Fatalities (immediate)	**All doses**	**>7000**	**>13 000**
Outpatient	**0.7-1.5**	**82 500**	**139 000**
Monitoring	**0.25-0.70**	**106 000**	**147 000**
Worried well	**<0.25**	**>150 000**	**>270 000**

*Table presents projected casualty estimates based on detonation of 1- and 10-kiloton nuclear devices. Assumptions include (1) a city with a population of 2 million people and (2) casualty estimates based on the Hazard Prediction Assessment Capability Program, version 3.21. Combined injuries consist of radiation injuries, burns, and blunt trauma. Modified from Waselenko et al [3].

or rapidly available. Variability in stem cell sensitivity also confounds clinical biodosimetry [6,7].

One management approach for intermediate-high dose exposure is to simply give comfort care, given that the historical outcomes have been poor. We would predict that for (6-10 Gy) radiation victims, families, and society as a whole would not accept this option, especially for younger adults and children. Use of growth factors is appropriate and granulocyte colony-stimulating factor (G-CSF) has been stockpiled in the United States. However, as discussed more fully below, G-CSF and other cytokines have limited effectiveness when given several days after radiation. In the case of a nuclear event, it is likely that it would take many hours, if not days, to estimate the radiation exposure for each patient; thus, for many, G-CSF will likely lose efficacy, especially in those who receive higher doses of irradiation.

Another approach is to plan an urgent allogeneic HCT. Complex logistics would require expedited HLA typing, rapid donor availability, access to available transplant beds, and prevention strategies for graft rejection, graft-versus-host disease (GVHD), and infection. Although these obstacles are formidable, the current era of HCT has produced techniques that are directly applicable to such situations. For example, it would be possible to perform nonmyeloablative cord blood or haploidentical transplantations as a bridge to autologous recovery or as definitive treatment. Thus, stem cell transplantation in this newer era of nonablative transplantation and improved supportive care could be applied if contingency plans were in place and their rapid activation were possible.

EVALUATION AND MANAGEMENT OF ACUTE RADIATION INJURY

Consequent to the terrorist attacks on the United States on September 11, 2001, many facets of terrorism preparedness are being examined. Unfortunately, planning and resource allocation for nuclear terrorism have not paralleled preparedness for other threats. The number of mass casualties that is generated consequent to a nuclear device detonation engenders skepticism. In the face of profound infrastructure loss, only contingency planning could enable prompt and proper identification of resource requirements, and personnel training needs to evaluate, support, and treat radiation victims.

The radiation threat can assume many forms, eg, industrial, medical, or military accident, terrorist radioactive "dirty" bomb, or an explosive nuclear device. The largest number of casualties would come from detonation of a fissionable weapon such as an improvised nuclear device. As presented in Table 1, even a small, 1-kiloton nuclear device would generate >300 000 victims in need of triage, with an anticipated ~85 000 who would develop some degree of acute radiation syndrome (ARS) and pancytopenia. Many of these victims will require early use of colony-stimulating factors and subsequently may require intense supportive care for their radiation-associated aplasia.

Briefly, radiation injury arising in such a setting may include external radiation that is delivered at a high-dose rate and external and/or internal contamination from exposure to the multitude of radioisotopes this is generated during the fission process. External decontamination is accomplished by removal of contaminated clothing and having the patient shower thoroughly with soap and water. Internal contamination may be clinically significant and lead to an increased risk of long-term carcinogenesis, but is unlikely to cause ARS.

OVERVIEW OF ARS

ARS, also known as radiation sickness, is defined as the signs and symptoms that occur after a whole-

body or significantly partial-body (>60%) exposure of >1 Gy that is delivered acutely at a relatively high-dose rate. Radiation damage primarily affects proliferating cells because they are the most sensitive to acute effects. The clinical components of ARS include hematopoietic, gastrointestinal, and cerebrovascular syndromes [3,7,8]. Symptoms of acute, high-dose radiation are dependent on the absorbed dose. They may appear within hours to days and follow a somewhat predictable course. The 4 phases of ARS are prodromal, latent, manifest, and recovery or death. Individuals after a lethal dose of radiation may develop a temporal compression of these phases into a period of hours, resulting in early death.

Because of the rapid cell turnover of lymphohematopoietic elements, these cells are among the most sensitive to radiation injury. Thus, the earliest presentation of ARS is the hematopoietic syndrome. ARS may be observed in patients who receive whole-body doses >1 Gy, but generally it is not clinically significant at doses <2 Gy [4] unless combined other injuries are present. Overlap of other organ damage with the hematopoietic syndrome would be observed if patients survive long enough to manifest their aplasia. Gastrointestinal mucosal barrier injury begins at doses of 5 Gy and can in itself be severe and life-threatening.

A significant partial- or whole-body dose >10 Gy is considered lethal. As depicted in Figure 2, dose-dependent myelosuppression develops over ≥1 week [7,8]. Dose-dependent extramedullary toxicity will also complicate management and increase mortality. Patients with radiation injury and burns or significant trauma have a combined injury syndrome, which is associated with a high mortality rate, even at lower radiation doses and lesser marrow injury. In a mass casualty scenario, such patients may be provided comfort care only.

Granulocytes may transiently increase in patients with <5-Gy exposure (Figure 2) [9]. This transient "abortive rise" before neutropenia may suggest a better prognosis. The nadir may occur between from 1 to 4 weeks [8,9], with a longer time to nadir at lower doses. These patients are still at high risk because their duration of neutropenia may be prolonged, requiring extended support with hematopoietic growth factors, blood products, and antimicrobials [10]. Patients with concomitant burns or traumatic injuries often show poor wound healing, bleeding, and infection [11].

Radiation exposure arising from an accident or a detonation will be inhomogeneous. Partial shielding from walls or furniture can leave reservoirs of viable hematopoietic stem cells. Some radioresistant accessory or stem cells may promote hematologic reconstitution [12,13].

Without aggressive medical support, the mean lethal dose of radiation leading to 50% mortality at 60 days is a whole-body radiation dose of ~3.5 Gy. This radiation dose increases to 6-7 Gy with optimal supportive care, antimicrobials, and transfusion support [8]. Survival requires hematologic recovery and trauma that is limited to survivable nonhematopoietic injuries.

Early triage should be based on the extent of trauma, burns, and other injuries. Although imperfect, clinical biodosimetry should be performed to estimate radiation exposure. It includes 3 elements: (1) time to onset of vomiting after exposure, (2) lymphocyte depletion kinetics, and (3) chromosomal aberration analysis [3,5,14,15]. By using Biodosimetry Assessment software (available as a free download at www.afrri.usuhs.mil), analysis of all 3 elements provides an estimate of the

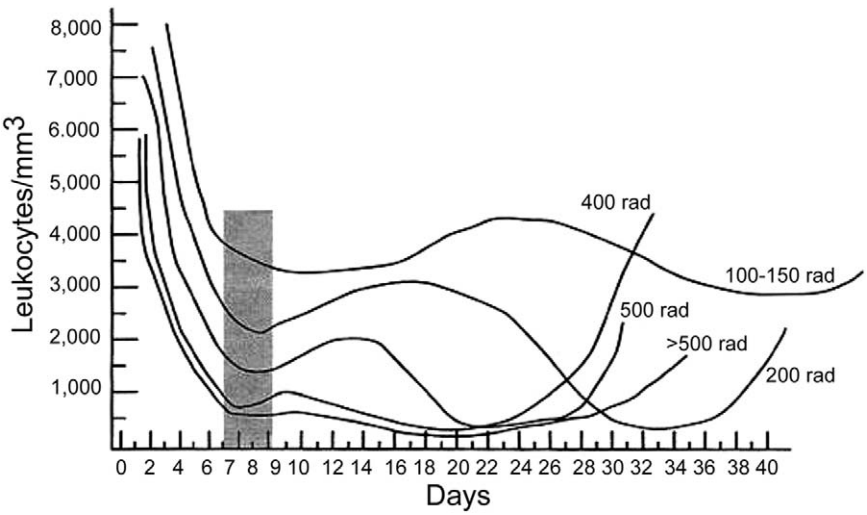

Figure 2. Leukocyte count based on exposure dose in patients who were exposed to radiation in Chernobyl. Note the abortive increase (transient increase before decrease) in leukocytes, which are primarily composed of granulocytes, in doses <500 rad (<5 Gy). Onset of neutropenia may not occur for weeks, especially with lower exposures, and duration of neutropenia may be prolonged. Reprinted with permission from Vorobiev [9].

Table 2. *Guidelines for Treatment of Radiologic Victims**

	Proposed Dose (Gy) Range for Cytokines	Proposed Dose (Gy) Range for Antibiotics§	Proposed Dose (Gy) Range for Referral for SCT Consideration
Small-volume scenario (≤100 casualties)			
Healthy individual, no other injuries	**3-10†**	**2-10‖ (if ANC <500/μL)**	**7-10 (for allogeneic SCT)**
Multiple injuries and/or burns	**2-6†**	**2-6‖ (if ANC <500/μL)**	**N/A**
Mass casualty scenario (>100 casualties)			
Healthy individual, no other injuries	**3-7†**	**2-7‖**	**7-10 (for allogeneic SCT)‡**
Multiple injuries or burns	**2-6‡**	**2-6†‖**	**N/A**

*Consensus guidance for treatment is based on threshold whole-body or significant partial-body exposure doses. Events due to a radiation accident or detonation of a radioactive device resulting in ≤100 casualties and those due to a detonation of a nuclear device resulting in >100 casualties have been suggested for consideration. Adapted from Waselenko et al [3]. ANC indicates absolute neutrophil count; SCT, stem cell transplantation, N/A, not appropriate due to poor outcome.

†Consider initiating at lower exposure in young children and the elderly. Initiate G-CSF or GM-CSF treatment in all who develop an ANC <500/μL.

‡If resources are available.

§Prophylactic antibiotics include a fluroquinolone, acyclovir (if seropositive for herpes simplex virus or medical history of herpes simplex virus), and fluconazole when ANC <500/μL.

‖ANC <500/μL. Antibiotics should be continued until neutrophil recovery has occurred. Follow Infectious Diseases Society of America guidelines [7] for febrile neutropenia.

patient's dose in grays. This estimate may then be used to determine a patient's risk for ARS, prognosis, and, most importantly, the need for hematologic support or transplantation therapy (Table 2).

MEDICAL MANAGEMENT OF RADIATION INJURY

Management of patients with ARS includes early use of hematopoietic cytokines (as discussed more fully below), antimicrobials, and transfusion support [3,14,15].

Early Phase (<72 Hours)

The medical needs in the first 72 hours must be directed toward trauma, burns, psychologic support, early initiation of G-CSF (5-10 μg/kg/d), and oral dosing with potassium iodide (130 mg/d for adults). In addition, patients who are likely to manifest ARS and have the potential to survive (estimated whole-body dose, >3-10 Gy but >2 Gy for children and the elderly) should be identified because they will require close monitoring and treatment with G-CSF.

Intermediate Phase (3-30 Days)

Because the time to onset and depth of neutropenia depends on dose, some patients will not develop neutropenia until several weeks later. Different degrees of neutropenia may persist for weeks to months.

Transfusion support with red blood cells and platelets is important as in any marrow aplasia. All cellular products should be depleted of leukocytes and irradiated to prevent transfusion-associated GVHD, which may be difficult to distinguish from radiation-induced fever, pancytopenia, skin rash, diarrhea, and hyperbilirubinemia.

Infections are a major cause of morbidity due to leukopenia and disruption of mucocutaneous barriers. Preclinical radiation models have demonstrated enhanced susceptibility to wound infection [16] and sepsis [17] with a smaller inoculum of bacteria compared with nonirradiated cohorts.

In animal models, quinolone-based prophylaxis [18-20] is effective in controlling gram-negative infections. Penicillin may add coverage for streptococci and further improve survival [21]. Therefore, extended-spectrum quinolones for prophylaxis against gram-negative and gram-positive infections are recommended [22]. Acyclovir is indicated for patients who are or were seropositive for herpes simplex virus. Prevention of herpes simplex virus reactivation is important because it may worsen mucositis and confound management of radiation injury.

Fluconazole can lessen invasive fungal infections and mortality in patients who undergo allogeneic bone marrow transplant [23,24] at daily oral doses of 200-400 mg. Fluconazole prophylaxis is ineffective against aspergillus, other molds, *Candida krusei*, and *Torulopsis glabrata*. Alternative antifungal therapy (caspofungin, voriconazole, or amphotericin) may be needed. As in other settings, management of neutropenic fever requires broad coverage of gram-negative bacteria including *Pseudomonas*, as detailed in recommendations from the Infectious Diseases Society of America [10,25].

Of major importance for prognosis and triage-based resource allocation is identification of victims with a poor chance of survival. The chance for survival

after irradiation with a dose >10-12 Gy is nil [26,27]. Such patients should be afforded comfort measures, pastoral care, and social support. This includes attention to pain management, antiemetics, antidiarrheals, and general comfort. Psychological support for the victim, family, and friends is essential.

Late Phase (>30 Days)

Little is known about immune reconstitution after inhomogeneous total-body irradiation at the high-dose rates evident after a nuclear detonation. Aberrant and incomplete immune reconstitutions are likely in some ARS survivors. Hypogammaglobulinemia and defects in cellular immunity may include prolonged lymphopenia, an aberrant lymphocyte repertoire, or defective lymphocyte function.

The risk of cytomegalovirus reactivation in seropositive patients is likely increased, so periodic monitoring for cytomegalovirus antigen or polymerase chain reaction should continue for 2-3 months after exposure for those patients who have had ARS with resultant leukopenia. For those with early evidence of cytomegalovirus infection, preemptive antiviral therapy should be employed. For those patients who continue to have T-cell immunodeficiency (ie, CD4 count $<50/\mu L$), ongoing monitoring may be appropriate. The risks of viral infection or other opportunistic pathogens, including *Pneumocystis jirovecii* (formerly *P carinii*), are unknown. Prophylaxis may be helpful.

Later monitoring and revaccination may follow guidelines similar to those recommendations by the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and the American Society of Bone Marrow Transplantation for transplant recipients [28].

ROLE OF GROWTH FACTORS IN RECOVERY AFTER RADIATION EXPOSURE

Whole-body irradiation is associated with organ toxicities that are related to dose. Hematopoietic damage is one of the most immediate complications. Victims who have this hematopoietic syndrome risk bleeding and life-threatening infectious complications. At exposure doses ≥6-8 Gy, victims will require a source of an allogeneic hematopoietic graft to replace damaged stem and progenitor cells. For victims who are exposed to lower doses, supportive care, with antibiotics and blood products, may enable recovery of endogenous hematopoiesis. In addition, growth factors may accelerate the recovery of hematopoiesis and improve outcome. Several hematopoietic growth factors (HGFs) studied in animal models include G-CSF, granulocyte-macrophage colony stimulating factor (GM-CSF), stem cell factor, interleukin 11 (IL-11), interleukin 1 (IL-1), and thrombopoietin (Tpo).

GRANULOCYTE COLONY-STIMULATING FACTOR

G-CSF is an HGF that acts selectively on the neutrophil lineage by stimulating progenitor cells to differentiate and can activate mature neutrophils. It is most often used for support of patients who receive chemotherapy to increase neutrophil recovery.

Tanikawa et al [29] studied the effects of recombinant human (rh) G-CSF in lethally irradiated mice and found an increased recovery of leukocytes, platelets, and hematocrit levels and improved survival. Hosoi et al [30] also evaluated the effects of rhG-CSF after whole-body irradiation and reported increased numbers of blood-circulating leukocytes, neutrophils, monocytes, and erythrocytes, but not lymphocytes or platelets. Nothdurft et al [31] studied a canine model of radiation by exposing animals to a single dose of 11.7 Gy. Treatment with rhG-CSF resulted in an early recovery to normal levels of granulocytes by day 11 after irradiation that was also associated with increased circulating progenitor cells within the first 8 days. Similar studies in primates have clearly demonstrated increased recovery of animals treated with rhG-CSF [32]. Because G-CSF approved for clinical use is readily available, it could be used for radiation victims in combination with supportive care of antibiotics and blood products. Because it has limited toxicity (bone aching), it has been the preferred agent for radiation victims [3,14].

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

The role of GM-CSF to increase recovery of hematopoiesis after irradiation is similar to that of G-CSF because GM-CSF also stimulates production of neutrophils. GM-CSF is approved for clinical use to increase recovery after bone marrow transplantation. Some toxicities that develop in patients who are treated with GM-CSF include local erythema, hypotension, chills, and fever. No formal comparative data with G-CSF are available.

INTERLEUKIN II

IL-11 is a stromal-derived HGF that stimulates thrombopoiesis and differentiation of bone marrow progenitor cells. In the United States, IL-11 has been approved by the Food and Drug Administration for the prevention of severe thrombocytopenia after myelosuppressive chemotherapy in patients who are at high risk of severe thrombocytopenia. The effects of

rhIL-11 were studied in irradiated rhesus monkeys [33]. Animals were exposed to total-body irradiation with a single 3-Gy dose and treated with 30, 60, or 120 μg/kg/d of rhIL-11 for 14 days. Treatment with IL-11 resulted in accelerated platelet recovery and higher platelet nadirs compared with placebo-treated controls. The investigators concluded that rhIL-11 may directly promote megakaryocyte development and ameliorate myelosuppression in irradiated animals.

However, treatment with rhIL-11 has been associated with significant adverse events including amblyopia, paresthesia, dehydration, skin discoloration, exfoliative dermatitis, and ocular hemorrhage. The extent of these adverse effects has limited the clinical use of IL-11.

THROMBOPOIETIN

Tpo acts primarily to regulate megakaryocytopoiesis and platelet production. It is also known as c-Mpl ligand and megakaryocyte growth and differentiation factor. Animal studies in mice [34] and primates [32] have evaluated the potential role of Tpo after radiation exposure. Tpo treatment resulted in multilineage hematopoietic recovery. Although the use of Tpo appears to be an effective treatment for victims of radiation exposure, the side effects and possible immunogenicity of Tpo analogies have limited its commercial development. Tpo is not currently approved for clinical use.

OTHER HGFS

Several other HGFs have been evaluated for an association with radiation exposure. Stem cell factor [35] and IL-1 [36] have been shown to have a radioprotective effect in animal models. When animals are treated with these HGFs before radiation exposure, recovery of hematopoiesis is accelerated and mortality is decreased. These HGFs have been reported to synchronize HSCs in S phase, resulting in decreased DNA damage and cell killing. This radioprotective effect may be an important factor when considering the safety of early response teams and protection during potential exposure to residual radiation.

COMBINATIONS OF HGFS

Many studies have evaluated the combined use of HGFs after exposure to radiation. Because HSCs require stimulation by combinations of HGFs to proliferate and differentiate, it may be necessary to provide multiple HGFs to obtain optimal recovery. In addition, because optimal recovery would involve rapid correction of neutrophil and platelet counts, treatment with ≥2 HGFs may be able to stimulate the granulocytic and megakaryocytic pathways. Several combinations have been evaluated: stem cell factor plus IL-1 [37], G-CSF plus GM-CSF [38], G-CSF plus Tpo [32], and IL-11 plus G-CSF [38-40].

Table 3. *Effects of Combined HGF Treatment in an Irradiated Nonhuman Primate Model**

Treatment	Duration (d)		Nadir (per μL)	
	Throm	Neut	Platelets	ANC
HSA	12.2	15.5	4000	2
rhG-CSF	6.7	12.3	9000	11
rhMGDF	0	13.3	43 000	38
rhG-CSF + rhMGDF	0.5	9.0	30 000	58

*Throm indicates thrombocytopenia; Neut, neutropenia; ANC, absolute neutrophil count; HSA, human serum albumin; MGDF, megakaryocyte growth and differentiation factor. Adapted from Farese et al. [32].

Farese et al [32] described the treatment of nonhuman primates with the combination of G-CSF plus Tpo (megakaryocyte growth and differentiation factor), which resulted in increased multilineage hematopoietic recovery. Durations of thrombocytopenia and neutropenia were decreased with the combination, as presented in Table 3. These data demonstrate the potential of this combination to decrease the duration and severity of thrombocytopenia and neutropenia.

The use of HGFs after exposure to radiation may have some therapeutic effect depending on the dose of radiation exposure and the time to treatment. Several HGFs show potential benefits in animal models, but the possible toxicities may limit their utility. The optimal HGF treatment may be some combination of HGFs for platelet and neutrophil recovery (eg, G-CSF plus Tpo). There is little information on T- and B-cell recovery after radiation exposure, and several cytokines may be effective in increasing immune recovery including IL-2, IL-7, and IL-15. Although immune deficiency may complicate radiation-induced myelosuppression, time to myeloid recovery may be critical for survival. Different cytokines might be needed to increase recovery of immune cells.

Although these are potential options for treating radiation victims with HGFs, there are no clear pathways that define optimal dosage, which also limit expected toxicities. Neither animal models nor feasible clinical trials can reliably predict responses in radiation victims. Empiric use of a best dose and treatment schedule to increase recovery requires follow-up with careful data collection and analysis for subsequent refinement of management guidelines.

CLINICAL TRIALS: A MODEL FOR CONTINGENCY PLANNING

Planning for contingencies involves definition of the possible problems, identification of requirements

for a response, detailing plans for action, and outlining required observations to assess the effectiveness of any intervention. Planning for the contingency of chemical, biological, or radiation exposures that lead to marrow damage and hematopoietic failure include multiparameter support and consideration of HCT. Outlining these contingency plans requires attention to evaluation of subjects at risk, requirements for needed intervention, plans for treatment, and follow-up assessments. Such contingency plans resemble the conventional elements of clinical research studies that are performed as phase II clinical trials.

We review the development of a clinical trial and how that protocol structure may serve the needs of contingency planning.

NECESSARY ELEMENTS OF A CLINICAL TRIAL

A successful clinical trial requires predefined subject eligibility, methods for consent, a defined treatment plan, specified follow-up measurements to enable assessment of success, and statistical measurements for comparison of the new intervention against an alternative, standard of care, or historical experience. Establishing these elements allows the clinical investigator to make observations on a defined subject population, interpret the results, and plan modifications for future trials.

Satisfactory clinical protocols require defined eligibility to characterize the subject population. This allows study observations to be generalized to a broader population with characteristics similar to the defined eligibility criteria, although outcomes may differ in subjects of different age, gender, and performance status as measured by organ function and preexisting morbidity or acquired complications. In subjects who are exposed to irradiation, the need for HCT may differ based on subjects' pre-existing health and severity of marrow failure. Important exclusions from clinical transplant protocols must include subjects who might recover from marrow injury without HCT or those with no available donor. Similarly, exclusions might delineate those with pre-existing trauma or severe infections, leaving them unable to survive the marrow insult and, hence, unlikely to benefit from any planned HCT.

The HCT study plan must also define a conditioning regimen, characteristics of the donor graft, and necessary supportive care sufficient to facilitate hematopoietic recovery. Marrow-damaging agents (radiation, mustard-based alkylators, or other myelotoxins) may be highly myelosuppressive yet have variable immunosuppressive effects. A neutropenic but still immunocompetent recipient might reject a graft, whereas a fully ablated, lymphopenic, and immunoincompetent recipient may require only minimally immunosuppressive supplemental conditioning to allow hematopoietic cells to engraft. Conceivably, as in the more controlled therapeutic HCT that is applied for treatment of cancer, differing conditioning might be necessary to satisfactorily engraft well-matched related donor progenitor cells versus partly or matched hematopoietic progenitor cells from a non-HLA identical, unrelated, or cord blood donor.

Necessary elements of supportive care must also be detailed to maximize the likelihood of subjects' survival until hematologic recovery. Antibiotics for prophylaxis and therapy, transfusion support, hematopoietic growth factors, hydration, nutrition, GVHD prophylaxis, and required isolation techniques need to be defined to deliver the critical components of supportive care even if contingency protocol therapy is to be delivered in diverse and dispersed treatment centers.

Follow-up measures to monitor recovery include serial measurements of donor lymphoid and myeloid chimerism, assessment of graft stability and durability, incidence and severity of GVHD, and measurements of immunologic reconstitution to determine the needed duration of antibiotic support. Observation for late events is also important.

Formal assessments of success include survival, secondary cancers, recovery from related complications, and important late effects of the HCT and from the initial marrow injury and associated trauma. All these elements must be followed in a defined schedule to identify frequent and rare events in survivors of successful marrow rescue therapy.

CLINICAL SCENARIOS RESEMBLING RADIATION OR EMERGENCIES REQUIRING HCT

Three clinical syndromes in which conventional myeloablative HCT is used include severe aplastic anemia, myelodysplastic syndrome, and severe combined immunodeficiency disease. In each syndrome, failure of marrow production leads to pancytopenia, with or without lymphopenia and immunocompetence. Subjects' clinical status and immune function before transplantation change the likelihood of success. Younger HCT recipients, even with serious comorbid complications, often tolerate intensive therapy with more resilience. Subjects with less well-matched donors require more immune suppression to overcome the greater histocompatibility difference between donor and recipient. However, the intensity of injury that accompanies ARS likely precludes consideration of a conventional myeloablative HCT.

The immune deficiency of the recipient, determined by the quantity and quality of original marrow toxic exposure, may predict the requirement for intensive immune suppression and need for peritransplantation conditioning to allow engraftment. Importantly, co-

existing trauma, multiorgan injury, and infections may modify the duration of support before transplantation and increase the likelihood of secondary complications developing before hematopoietic recovery. Coordination of HCT and trauma management expertise in such planning is essential.

CURRENT TRANSPLANT PROTOCOLS AS MODELS FOR EARLY PREPAREDNESS

Patients with severe aplastic anemia or myelodysplastic syndrome who receive HCT have pancytopenia and relative immunocompetence that may occur in radiation victims. These patients can be treated with decreased intensity, but highly immunosuppressive (nonmyeloablative) conditioning, which may model a contingency protocol for acute radiation or myelotoxic chemical injury.

A suitable contingency protocol must be prepared in advance. It must be reviewed, modified, and established in the preparedness network to allow prompt activation when subjects require urgent treatment. A multicenter protocol also needs prospective data collection to allow subsequent assessment, interpretation of results, and plans for future refinement. As such, the enrolled subjects, although they are treated according to predefined treatment plans that reflect best practice and sophisticated supportive care, are also human subjects who need protection of their privacy and respect for their opportunity to consent or decline participation in the prospective data collection plan. The contingency treatment protocol, therefore, needs review and approval by relevant institutional review boards, perhaps allowing exemption from yearly reapproval if no emergencies and thus no subjects yield any accrual.

This contingency plan must also be reviewed, modified, and approved by hematopoietic cell donor centers and cord blood banks to establish procedures that are needed for urgent searching and donor availability. These donors, who also are research subjects in this prospectively planned treatment and data collection protocol, need consent for their participation. Similarly, their clinical management protocols might be exempt from yearly reapproval by an institutional review board if no emergency donors are requested. Under any circumstances, emergency preparedness protocols need periodic re-review for re-evaluation and modification as appropriate.

BARRIERS TO CONTINGENCY TRANSPLANT PLANNING

Successful implementation of a contingency transplantation therapy protocol requires a pre-existing committed network with developed, distributed, and actualized plans ready to initiate treatment. Financial planning needs to be in place to support commitment of resources from hospitals and physician practice groups to overcome the barriers and delays of conventional pretransplantation financial approval. Similarly, availability of hospital beds, prompt identification of suitable HLA-compatible donors, and facilitation of donor cell collection and transport needs preapproval and planning. Contingency protocols will require a safe, available blood supply, pretransfusion irradiation to prevent transfusion-associated GVHD, and a necessary supply of relevant pharmaceuticals (immunosuppressives, antibiotics, HGFs), and other requirements for best-practice supportive care.

Development of effective contingency protocols will require committed participation from transplantation centers and their institutions and formal evaluation of the prototypic clinical scenarios that yield similar myelotoxic exposures to develop safe, effective, and feasibly implementable contingency plans. The planning process will require development, re-evaluation, and rewriting of the contingency protocol as clinical experience in conventional transplantation evolves and supportive practices advance.

SUMMARY

Uncertainty remains about the number of victims who would develop ARS and clinically meaningful pancytopenia consequent to a nuclear detonation. Nonetheless, transplantation physicians, hematologists, and oncologists are challenged to prepare for a role in the management of patients with ARS in the event of a regional, national, or international emergency. We can hope that radiation accidents or attacks do not occur, but we must improve our preparedness because they might.

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