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Review Article

Role of Haematologist in Radiologic and Nuclear Events

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In Nuclear disasters whether they happen in war or occur accidentally the results are always very devastating. Following a Nuclear disaster all doctors, along with haematologists would be called out to participate. It is imperative to develop treatment guidelines for post radiation emergencies. Though such guidelines are available all around the world we outline the current plans for event response including catastrophic events that would require extensive support.

The threat of possible nuclear disaster whether due to detonation of a nuclear device or due to accidents in handling of the radioactive materials requires that we develop and implement a plan of response.[1] More than 400 radiologic accidents have occurred since 1944, resulting in more than 3000 significant exposures. Approximately 10 million "sealed sources" of radioactive material (e.g., cesium-137, cobalt-60) are used for medical, industrial, agricultural, and research purposes worldwide. More than 600 of these were lost or stolen since 1995 and less than half were eventually recovered.

The haemopoietic system is the most rapidly dividing tissue of the body and as such the most vulnerable of all and most radiosensitive. Exposure of the haemopoietic stem cell as well as the progenitor cells results in their exponential death. The haemopoietic progenitor cells cannot survive a dose of >2-3 Gray (Gy).It results in haematological disaster in subsequent days including lymphopenia, bone marrow atrophy ,pancytopenia and bleeding which all contribute to its lethality. [2]

Models suggest that, if a device similar to the bomb detonated over Hiroshima struck a city such as Karachi up to 175 000 victims would require intensive medical care and 300 000 would require management for myelosuppression. [3]

Establishing National Haematology Radiation Injury Treatment Organization

It is purposed that a Pakistan Haematology Radiation Injury Treatment Organization be established on the lines of Radiation Injury Treatment network (RITN) in the United States which was raised in the year 2001.[4]

The scope of Pakistan Haematology Radiation Injury Treatment Organization (PHRITO) would be as follows: [5]

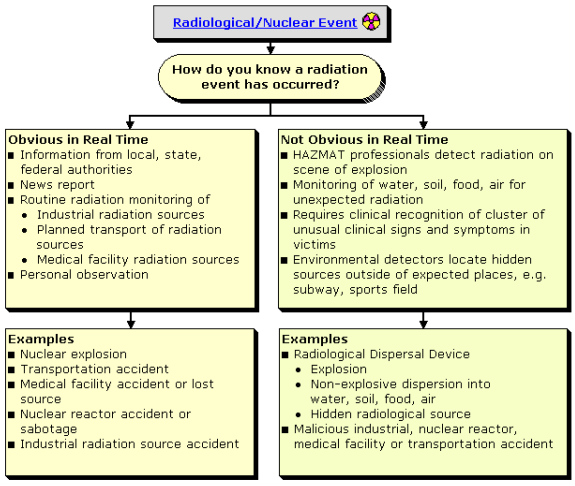
1. To develop treatment guidelines for managing haematologic toxicity among victims of radiation exposure
2. To educate healthcare professionals about pertinent aspects of radiation exposure management
3. To coordinate situation response after a radiation event
4. To provide comprehensive evaluation and treatment for victims at participating HSCT centers.

What a Haematologist needs to know in case of Radiation Event

1. Discovering an Event:

Several types of events can result in radiation exposure. A Haematologist must posses a basic knowledge about the spectrum of potential events involving radioactive material.

Table 1 Algorithm for discovering Radiation event [6]



Several types of events could result in radiation exposure. Intentional events can involve radiologic exposure devices (REDs), radiologic dispersion devices (RDDs), and improvised nuclear devices (INDs). An RED is a radioactive source placed surreptitiously in a public space or other location. [7]

2. Triage after a radiation event

Healthcare organizations have prepared their responses to radiation events for triage, transportation, and treatment of victims after an IND.The triage comprises four basic steps.

First, Life threatening injuries must be dealt at once. The patients should be stabilized and shifted to a Medical facility and it should be presumed that the patients are contaminated.

Second, Preliminary decontamination be performed.

Third, Triage for Adults (START) and Children (JumpSTART) is started. Initial samples should include CBC, Blood chemistry and a sample for cytogenetics if required later. [8]

Coloured tags are assigned to individual patients sorted out according to the severity of injury.

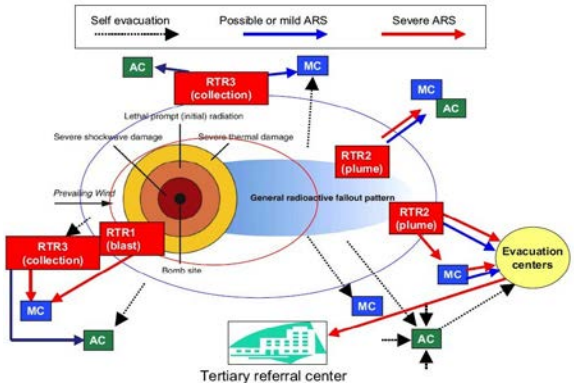


Fig 1: Organization of triage centers

Triage centers are located in concentric rings around the affected area, providing initial stabilization and decontamination (RTR1-RTR3), more extensive Medical Care (MC), and rapid screening of unexposed or minimally exposed individuals at Assembly Centers (AC). Patients who require further care are evacuated to referral centers in unaffected regions (fig 1). [9]

A conceptual model for triage, transportation, and treatment of victims after an IND, the RTR system (Radiation Triage, Treatment and Transportation) has been developed. Briefly, the initial triage and patient decontamination will occur at RTR sites, whose location and resources will be determined by incident commanders. RTR1 are near the blast andRTR2 are near the plume, both within areas of residual radiation. In contrast, RTR3 will be located outside the region with significant residual radiation. Based on previous radiation accidents, the number of unirradiated persons who seek medical attention after an event could dwarf the number exposed. For example, when scavengers in Goiania, Brazil, procured an improperly secured caesium source resulting in 28 cases of radiation sickness, more than 112 000 people presented for screening at the nearby Olympic stadium.Victims requiring further care may be transferred to Medical Care (MC) sites located outside of the disaster zone. [10]

I. Role of Haematologist in Acute Radiation Injury

Acute radiation syndrome (ARS) can affect virtually any organ but primarily manifests as injury to rapidly dividing tissues. The severity of the ARS varies accordingly with the radiation dose .The clinical course of ARS generally includes a prodromal phase, followed by a period of apparent remission, manifest illness and ultimate recovery or death.[11]

The haematopoietic syndrome develops between the doses of 3-8 Gy.Low dose exposure of<2 Gy produces cytopenias but does not cause significant bone marrow damage. Peripheral blood lymphopenia develops within 6-24 hours. Radiation induces apoptosis and alters recirculation of lymphocytes. Based on the counts of peripheral blood lymhocytes, granulocytes, platelet count and blood loss, the haemopoietic response to radiation can be divided in different groups

Role of Biodosimetery

Treating Haematologists will be required to calculate radiation dose using the information they have. Forms of biological dosimetery include lymphocyte depletion kinetics, interphase aberrations induced by okadaic acid and p34cde^2 /Cyclin B kinase and electron spin resonance of dental enamel.

Monitoring for a decrease in absolute lymphocyte count has been found to be a reliable and practical method to assess soon after radiation exposure.Andrews et al have developed lymphocyte depletion kinetic curves which predict pattern of early lymphocyte response in relation to dose. Whenever possible in cooperation of data from three key elements, time to onset of vomiting, lymphocyte depletion kinetics and chromosome aberrations are required for assessment of prognosis and selection of therapy. Patterns of lymphocyte response define stages stretching from normal to lethal.[12]

The frequency of chromosomal aberrations in lymphocytes correlate well with the radiation dose. The formation of dicentrics involves an interchange between two separate chromosomes (fig 2). Ring

formation involves a break in the arm of a single chromosome followed with the rejoining to form a ring and a fragment.

Chromosomal aberrations have become the gold standard in dosimetery.Their detection is facilitated by the application of hybridization probes for centromeres and automated metaphase detectors.

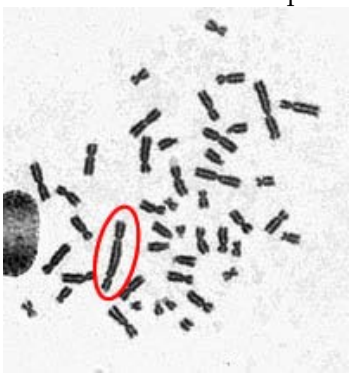


Fig 2: Dicentric chromosomes after nuclear injury

II. Management of Haematological Complications

Cytopenias and Growth Factors

Post radiation exposure cytopenias develop after 6-24 hours. Lymphocyte count is first to fall. There is a major decrease in the count of helper T cells. Irradiation to the bone marrow stem cells and the progenitor cells results in exponential death.Mitotically active haemopoietic cells are unable to divide after a dose of >2-3 Gy which leads to a haematological crises in the coming weeks. The result is lymphopenia, bone marrow atrophy pancytopenia and its attendant sequele: infection, bleeding and poor wound healing which contribute to its lethality. Sometimes pockets of radiation resistant stem cells are left behind. These stem cells play an important role in the recovery of the haematopoiesis after radiation dose exposure as high as >6 Gy. [13,14]

Haemopoietic colony stimulating factors like G-CSF, GM-CSF and PEG-G-CSF have shown to be effective in radiation induced bone marrow aplasia.Their enhancement of neutrophil recovery and most importantly their survival benefit as observed in carefully conducted clinical trials has shown them to be effective in patients of post radiation marrow aplasia.

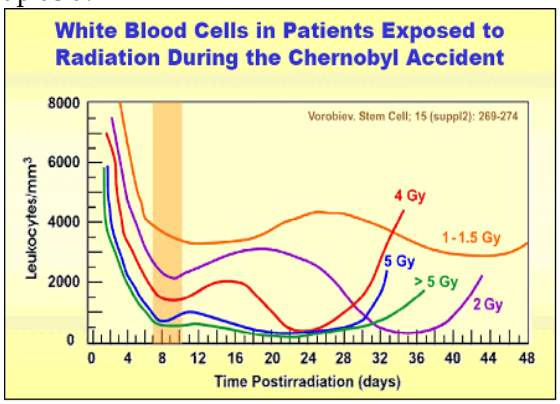


Fig 3: White blood cells count post radiation accident

A number of studies examining the role of G-CSF,GM-CSF, pegylated G-CSF, and a chimeric molecule in an irradiated rhesus macaque's model demonstrated significant neutrophil enhancement when these agents were employed on day 1 post exposure and continued for 14-21 consecutive days.[15]

Use of blood products:

High-dose whole body radiation exposure induces haematopoietic cytopenias potentially requiring transfusion of blood products. Cytopenias requiring transfusion occur typically 2 to 4 weeks after high-dose radiation exposure, although time to nadir varies by patient, exposure dose, and dose rate. Blood loss requiring transfusion may also result from trauma associated with the radiation incident and gastrointestinal losses from a variety of causes. Cellular blood products that will be transfused to radiation victims should be, preferably, leucodepleted and/or irradiated, most importantly to prevent post transfusion graft versus host disease (PT-GVHD)

Avoid transfusions from first-degree relatives whenever possible because it increases the risk of PT-GVHD. If no other option is available, this blood must be irradiated. Transfusion of fresh blood especially that stored for fewer than 3 days should be avoided whenever possible, except for platelet concentrates.

The fresher the blood, the higher the risk of PT-GVHD, especially with blood used within 3 days after donation. Typical PT-GVHD presents with fever, generalized erythema 1 or 2 weeks after transfusion, followed by liver dysfunction, diarrhoea, and bone marrow failure with pancytopenia. Most patients die of multi-organ failure within 1 month of transfusion. PT-GVHD occurs at a higher rate in patients with no

history of blood transfusions and in patients who receive blood from relatives. [16]

Leukocyte reduction by filtration is not sufficient to prevent PT-GVHD, but it is recommended because it diminishes the febrile non-hemolytic reactions,immunosuppressive effects of blood transfusions platelet alloimmunization and cytomegalovirus infection . Blood and blood product irradiation will prevent PT-GVHD. Both irradiation and leukocyte reduction are recommended when these are available.

Platelet transfusion guidelines

The benefits of pooled platelets or single donor platelets are similar; the two products can be used interchangeably. Single donor platelets from selected donors are preferred when histocompatible platelet transfusions (i.e., HLA-A and HLA-B antigen matched) are needed. [17]

Granulocyte transfusion guidelines

Granulocyte transfusions should be considered for severely neutropenic patients (ANC <200/uL) when infection persists despite optimal antimicrobial and supportive therapy.

Daily transfusions for a period of several days to weeks are guided by 24-hour WBC determinations and clinical response. Prophylactic transfusions have not been shown to reduce morbidity or mortality. [18]

III. Supportive Care

For those who experience significant neutropenia (ANC < 500/µL) broad spectrum prophylactic antimicrobials should be employed as the neutropenic duration is likely to be prolonged. Prophylaxis should include a fluroquinolone (FQs) with streptococcal coverage (with penicillin or amoxicillin if not inherently covered by the FQ), as an antiviral agent if the patient is herpes simplex virus (HSV) positive, and an antifungal agent. Studies in irradiated mice have demonstrated that the gut flora also undergoes a dose-related reduction within the first 4 days post-radiation. This is followed by a relative increase of Enterobacteriaceae compared to anaerobic bacteria by the 12th day. Fatal bacteraemia may then result from the bacterial translocation of these organisms. [19]

During the intense periods of immunosuppression, these patients are at high risk for HSV reactivation, which may be confused with radiation stomatitis and may complicate its management. can mimic or add to the severity of mucosal injury. Therapy of patients with neutropenia and infection should be guided by the recommendations of the Infectious Diseases Society of America (IDSA) and should take into consideration other foci of infection such as mucosal or integument injury.[20]

Potassium Iodide

Owing to their short half-lives, radionuclides are unlikely to be components of an RDD or "dirty bomb." Therefore, iodine prophylaxis is not indicated. Nevertheless, for an incident involving a nuclear power plant or an IND, it is probable that radioiodine will be released. Early prophylaxis is indicated in the latter situation. The thyroid is a radiosensitive organ at risk. Exposure to radioiodine can result in thyroid cancer, a delayed consequence, which may be more aggressive than de novo forms. Exposure could begin immediately if the released plume is near ground level. The main route of radioiodine exposure is inhalation in those in the near field and via ingestion of contaminated food and drink (particularly milk) for those further away (far field). Exposure via the latter route could last longer, cover a larger area, and affect a larger population. Thyroid blocking with potassium iodide (KI) affords protection when radioisotopes of iodine are components of the exposure. Oral administration of KI should be given as soon as possible after exposure (within 6 hours). Caution should be taken with those individuals who are allergic to iodine because severe reactions have been reported. KI should be dosed daily, until the exposure risk no longer exists. [21]

Role for stem cell transplantation

Some victims of a large-scale event may receive sufficient doses of radiation to cause irreversible myeloablation. These patients will commonly have multi-organ damage. What remains unclear is whether allogenic HSCT can be a life-sustaining measure in this setting. To date, 31 patients have undergone allogenic HSCT after accidental radiation exposure. Median survival after transplantation for these patients is approximately 1 month. Only 4 patients survived 1 year reconstituted autologous haematopoiesis, raising the question whether the HSCT provided any benefit. [22]

Particularly troubling was the contribution of graft-versus-host disease to mortality in more than 20% of patients. In many regards, patients with myeloablation from radiation exposure are similar to those with aplastic anaemia. A reduced intensity conditioning regimen for severe aplastic anaemia (where immunosuppression but not myeloablation is required) is being tested in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN Protocol 0301).

The complex nature of radiation injury is such that no single drug provides benefit in all circumstances and against all aspects of radiation injury. Antioxidants and radioprotectants are presumably most effective if present at the time of irradiation, whereas therapeutics such as growth factors may target one or more but not all affected organ systems. For this reason, many experts think that combination therapy will be required to produce substantial improvements in outcomes.[22]

Conclusion

The widespread availability of radioactive material has made future exposure events, accidental or intentional, more likely . Haematologists, oncologists, and HSCT physicians are uniquely suited to care for victims of radiation exposure, creating a collective responsibility to prepare for a variety of contingencies.

Government of Pakistan should establish Haematology Radiation Injury Treatment Organization (PHRITO) .The Organization should be involved in the planning to deal with Radiation injuries. Although the logistical difficulties inherent to any large-scale response are enormous, the potential for lifesaving measures is equally grand. PHRITO should standardize approaches to Biodosimetery, evaluation, and treatment. The protocols should be available for review, comment, and further development. PHRITO should focus on streamlining these processes, providing training to medical practitioners around the country, and validating medical countermeasures to reduce the morbidity and mortality of radiation exposure.

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