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REVIEW ARTICLE

Radiation hazards of the Ukraine nuclear power plants: how can international blood and marrow stem cell transplant societies help?

Shahrukh K. Hashmi[1,2,3] · Ray C. Powles[4] · David Ma[5] · Ibrahim N. Muhsen[6] · Mahmoud Aljurf[7] · Dietger Niederwieser[8,9] · Daniel J. Weisdorf[10] · Mickey B. C. Koh[11,12,13] · Hildegard Greinix[14]

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Abstract
Any conflict in countries that process nuclear power plants raises concerns of the potential radiation injuries to the people in that region and beyond such as the current conflict in Ukraine. International healthcare organizations and societies should prepare for the potential scenarios of nuclear incidents. The Worldwide Network for Blood and Marrow Transplantation (WBMT) and its members, have recent experience preparing for this type of events such as the Fukushima incident in 2011. In this article, we discuss the risks of radiation exposure, current guidelines, and scientific evidence on hematopoietic support, including the role of hematopoietic stem cell transplant (HCT) for those exposed to nuclear radiation, and the role that the WBMT and other global BMT societies can play in triaging and managing people suffering from radiation injuries.

Keywords Ukraine · Nuclear · Radiation · Transplant · Stem cells

Introduction

The current conflict in Ukraine is causing humanitarian and health care crises. Millions of Ukrainians are now being displaced in Ukraine and in neighboring countries as refugees or internally displaced people, including hundreds of thousands of cancer patients [1–3]. Since the development of nuclear technology, multiple accidents have occurred, for reasons such as war (e.g., Hiroshima and Nagasaki), accidents (e.g., Chernobyl), or environmental disasters (e.g., Fukushima). Another major nuclear accident becomes a small, but real possibility particularly with the recent fights close to Europe's biggest nuclear plant, Zaporizhzhia plant, which led to the plant being disconnected from Ukraine's electricity grid [4]. Thus, international organizations,

Shahrukh K. Hashmi, Ray C. Powles, and David Ma are co-chairs of the Global Emergency/Nuclear Accident Management Committee, the WBMT.

✉ Shahrukh K. Hashmi
Hashmi.Shahrukh@mayo.edu

Ray C. Powles
myeloma@clara.co.uk

1 Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN, USA

2 Department of Medicine, Sheikh Shakbout Medical City, Abu Dhabi, UAE

3 College of Medicine & Health Sciences, Khalifa University, Abu Dhabi, UAE

4 Cancer Centre London, 49 Parkside, Wimbledon, London SW19 5NB, UK

5 Department of Haematology, St Vincent's Hospital, Darlinghurst, NSW, Australia

6 Section of Hematology and Oncology, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

7 Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

8 University of Leipzig, Leipzig, Germany

9 Aichi Medical University, Nagakute, Japan

10 Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA

11 Infection and Immunity Clinical Academic Group, St George's University of London, London, UK

12 Department of Haematology, St George's University Hospitals, London, UK

13 Cell Therapy Programme, Health Sciences Authority, Outram, Singapore

14 Division of Hematology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

particularly healthcare organizations, must stay vigilant and prepared to provide the appropriate humanitarian support to alleviate potential catastrophic consequences of such an accident.

This article focuses on a coordinated hematopoietic stem cell transplant (HCT) service in the case of an ionizing-radiation disaster provided by the members of the Worldwide Network for Blood and Marrow Transplantation (WBMT) Global Emergencies/Nuclear Accident Management Committee. We discuss possible hematopoietic support, including the role for allogeneic HCT, and the roles that global professional HCT societies can play in case of any nuclear accidents.

Ukrainian nuclear program: an introduction

Ukraine has four active nuclear power plants and 15 nuclear reactors, which supply more than 50% of the country's electrical power. This makes it one of the countries that rely mostly on nuclear energy generating about 154 Terawatt-hours (TWh) in 2019 [5]. Its nuclear program is governed by the National Nuclear Energy Generating Company of Ukraine (Energoatom). The four plants are located throughout Ukraine. Many of those reactors were stopped since the start of the conflict [6].

Ukraine had suffered from nuclear accident catastrophes in the past, with the Chernobyl disaster in 1986 that affected millions of people leading to both mortality and lasting morbidity. However, the exact extent of the effects is unknown, given the limits of epidemiologic surveillance, plus a lack of transparency and data sharing but many studies have reported the increased risk of radiation-related long-term health consequences, including cancers [7, 8].

The current conflict in Ukraine raises concerns about the infrastructure, security, and safety of the Ukrainian nuclear program. Since the start of the conflict, multiple attacks took place near the Zaporizhzhia power plant and the International Atomic Energy Agency (IAEA) reported that the power plant was shelled, causing a fire [4, 9]. This did not affect the reactor but raised concern about the potential of future radiation accidents that might lead to severe consequences. The viewpoint from experts suggests that the power plants are sufficiently advanced with multiple levels of safety measures, making a nuclear catastrophe less likely [10]. Additionally, the reactors have mechanisms to prevent any accidents from power grid loss, as their backup sources were improved after the Fukushima accident [11]. However, besides a direct accident at the nuclear reactors, the spent fuel storage is an area of concern for a potential catastrophic ionizing-radiation disaster.

Multiple European and international organizations are monitoring the situation closely including IAEA, World Health Organization (WHO), UK Health Security Agency and Institut de radioprotection et de sûreté nucléaire (IRSN). The IAEA provides daily updates through their Nuclear Safety and Security in Ukraine webpage (https://www.iaea.org/nuclear-safety-and-security-in-ukraine). In conflicts which have a potential of a nuclear disaster, the professional PB stem-cell-transplant societies can play a major role advising on hematologic care and hematopoietic support including salvage HCTs for people exposed to a dangerous level of ionizing radiation. The exercise for preparedness was well documented by the European Society for Blood and Marrow Transplantation (EBMT) in 2011 during the Fukushima disaster [12, 13].

General and hematologic radiation effects

Exposure to any nuclear radiation leads to many short and long-term adverse effects [14], depending on the amount and duration of radiation exposure. Victims may develop acute radiation syndrome in the immediate and brief period after exposure (< 48 h). They will exhibit various symptoms, including skin burns and thermal injuries, infections, bone marrow failure (e.g., leukopenia, anemia), and gastrointestinal symptoms (e.g., vomiting, bloody diarrhea). High levels of acute exposure at lethal doses can lead to immediate or acute death, mainly due to thermal burns, cardiovascular collapse, gastrointestinal involvement, and bone marrow failure [15–17]. These are the results of cell death caused by the "deterministic effects" of radiation. Some of the effects related to these deterministic effects can present later, resulting in eye and cardiac manifestations [18].

The effects of radiation exposure are not limited to the acute phase, as many long-term effects were reported in the literature years after exposure, including psychological effects, such as depression and anxiety. The physical effects are caused by radiation "stochastic effects" leading to genetic damage and gene mutations [18]. The Life Span Study of the Hiroshima and Nagasaki atomic-bomb survivors showed an excess relative-risk for malignancies [19]. For instance, excess cases of leukemia were reported in both children and adults, three years after the incident [20]. Survivors were also at higher risk of myelodysplastic-syndrome [21]. Solid cancer was also common in atomic-bombing survivors with an increased risk of most solid cancers [22, 23]. The studies demonstrated an increasing risk proportional to the increase in radiation exposure (even at moderate levels of ionizing-radiation exposure) and higher risks in children. On the other hand, studies reported an increased risk of thyroid cancer due to exposure to radioactive iodine; however, risk for other cancer types was not proven [24, 25].

Acute radiation exposure can lead to acute BM suppression that manifests as leukopenia, thrombocytopenia, and anemia even at doses lower than 2 Gy. However, higher doses are needed to lead to hematopoietic-stem-cell (HSC) damage and BM failure. Lymphopenia is usually noticed in the early hours after exposure, and lymphocyte depletion kinetics remains one of the simplest and most predictive markers of the effects of ionizing-radiation on the BM [26]. The degree of lymphopenia is reflective of mortality [17, 27]. HSCs are very sensitive to ionizing-radiation. For instance, individuals exposed to total body irradiation (TBI) of ≥ 6 Gy can lead to the death of almost all BM stem cells [26] although the dose rate and inhomogeneity of the exposure modify the biologic effects.

Primary triaging

In every nuclear accident scenario, people at risk should firstly receive primary triaging. This involves moving them away from the radiation source. We would like to refer the readers to the updated recommendations by the IAEA on their website.

Primary triaging centers should be near the incident site if safe from ongoing exposure and should provide initial stabilization and decontamination of victims. First responders should have the tools to identify victims who might need further assessment and arrange their transfer to more appropriately equipped centers.

It is very important to note that many organizations provide information for response during such incidents, including templates and guidelines for triaging, decontamination, and specifics on treatment. Examples include RENEB (Realizing the European Network of Biological Dosimetry), US RITN, and Radiation Emergency Medical Management (REMM), all of which provide information through their websites (REMM have created a mobile application too) [28–30]. Figure 1 includes a list of websites that provide important information regarding response to nuclear incidents.

Medical evaluation and monitoring after radiation exposure

In 2005, the EBMT consensus meeting recommended the use of Medical Treatment Protocols for Radiation Accident (METREPOL) [31]. This recommendation was based on data from victims of prior nuclear accidents [32, 33]. The assessment of the severity of injury begins with prodromal symptoms, which might include severe erythema, loss of consciousness, gastrointestinal (GI) symptoms (early vomiting or diarrhea), fevers, and hemodynamic instability, all of which can be indicative of severe injury; however, this phase might be missed if exposure is unknown [31, 34].

METREPOL assesses effects on four organ systems, namely neurologic, gastrointestinal, hematopoietic, and cutaneous and categorizes responses into four categories 1–4, with 1–3 indicating likely reversible damage and 4 indicating a low likelihood of reversibility. For instance, hematologic effects under METREPOL (see Table 1) are categorized from H1-H4 (H stands for hematologic), with H1 including patients with lymphocyte count of $\geq 1.5 \times 10^9$/L, neutrophils count of $\geq 2.0 \times 10^9$/L, platelet count of $\geq 100 \times 10^9$/L. They do not need antibiotics and have normal hemoglobin with no blood loss except for petechial and easy bruising. On

Panel 1: Suggested websites and organizations that provide material and resources on risk assessment, planning, decontamination, victims, triaging.

- WHO- Radiation Emergency Medical Preparedness and Assistance Network (Website: https://www.who.int/groups/rempan).
- International Atomic Energy Agency (Website: https://www.iaea.org/), updates regarding Ukraine can also be accessed through: Nuclear Safety and Security in Ukraine webpage (https://www.iaea.org/nuclear-safety-and-security-in-ukraine)
- EBMT- Nuclear Accident Committee (Website: https://www.ebmt.org/nuclear-accident-committee)
- The Radiation Injury Treatment Network (Website: https://ritn.net/)
- Radiation Emergency Medical Management (Website: https://remm.hhs.gov/), also provides an application that is available on both Macintosh and Android systems.
- Institut de radioprotection et de sûreté nucléaire (Website: https://www.irsn.fr/FR/Pages/Home.aspx)

Many of the above websites provide materials and updates in multiple languages.

Fig. 1 Suggested websites and organizations that provide material and resources on risk assessment, planning, decontamination, victims, triaging

Table 1 The assessment of the hematopoietic system according to METREPOL [29, 32]

Parameter	Level 1	Level 2	Level 3	Level 4
Lymphocyte count	$\geq 1.5 \times 10^9$/L	1- 1.5×10^9/L	0–5-1×10^9/L	$< 0.5 \times 10^9$/L
Granulocyte count	$\geq 2.0 \times 10^9$/L	1–2×10^9/L	0.5–1×10^9/L	$< 0.5 \times 10^9$/L or initial granulocytosis
Platelets count	$\geq 100 \times 10^9$/L	50–100×10^9/L	20–5-$\times 10^9$/L	$< 20 \times 10^9$/L
Blood loss and hemoglobin (Hb) level	No blood loss, only petechiae and bruising (Hb is normal)	Minimal loss of blood (Hb decrease: < 10%)	Gross loss of blood (Hb decrease: 10–20%)	Spontaneous bleeding and moderate to severe loss (Hb decrease: > 20%)
Evidence of infection	None or possibly local (no antibiotics needed)	Local infection (only topical/local antibiotics needed)	Systemic infection (oral antibiotics needed)	Sepsis (intravenous antibiotics needed)

the other hand, patients categorized as H4 will have features including lymphocyte count of $< 0.5 \times 10^9$/L, neutrophils count of $< 0.5 \times 10^9$/L or initial neutrophilia (neutrophils might increase initially and then start to decline), platelet count of $< 20 \times 10^9$/L. These patients will usually be septic with spontaneous bleeding and > 20% decrease in their hemoglobin levels [31]. To aid in triaging victims effectively in the first 48 h, the consensus recommends the use of a scoring system with level 1 indicating less severe injury and outpatient follow-up, level 2 indicating the need for hospitalization and level 3 predicting the development of multi-organ failure with the need for a higher level of care [31, 34]. The scoring system is shown in Table 2 and is published on the EBMT Nuclear Accident Committee webpage (https://www.ebmt.org/nuclear-accident-committee). Similar guidance documents and management tools are available through RITN and REMM websites [29, 30]. However, it is very important to consider the dynamic nature of these counts as blood counts might be high initially (abortive rise) before decline [27]. Furthermore, many studies have developed models and softwares that are able to aid in predicting outcomes in patients [35, 36]. For instance, Port et al. (c35) developed a model using blood counts to predict outcomes in patients after radiation. The model was able to discriminate between unexposed and irradiated completely and the results showed that day 1 lymphopenia is a more accurate predictor compared to neutrophils/platelets and that the accuracy increased with longer follow-up (day

Table 2 Suggested primary triaging system, adapted from the WHO consensus meeting and the EBMT pocket guide [29, 32]

	Score I	Score II	Score III
History and physical examination findings			
Mean time to symptoms appearance	< 12 h	< 5 h	< 30 min
Skin erythema	No	Possible	Yes (severe) and appears in < 3 h
Weakness	Yes (Mild)	Yes (Moderate)	Yes (severe)
Nausea	Yes	Yes (Severe)	Usually not
Vomiting frequency in 24 h	< 1	1–10	> 10
Diarrhea frequency in 24 h	< 3 (Bulky consistency)	2–9 (Soft)	≥ 10 (watery)
Abdominal pain	Minimal	Intense	Excruciating
Headaches	No	Yes	Severe*
Fever	< 38	38–40	> 40
Blood pressure	Normal	Possible temporary hypotension	Hypotension (SBP < 80)
Loss of consciousness	No	No	Yes (can be coma)
Laboratory findings			
Lymphocyte count at 24 h	$\geq 1.5 \times 10^9$/L	$< 1.5 \times 10^9$/L	$\geq 0.5 \times 10^9$/L
Lymphocyte count at 48 h	$\geq 1.5 \times 10^9$/L	$< 1.5 \times 10^9$/L	$\geq 0.1 \times 10^9$/L
Management recommendations			
Management settings	Outpatient management	Necessitate hospitalization	Necessitate hospitalization (likely need critical care due to MOF)

Abbreviations: *SBP*, systolic blood pressure; *MOF*, multi-organ failure

*Can also indicate intracranial hypertension and bleeding in some cases

1 vs day 3). Such approaches might be important as it takes into account the evolution of laboratory and clinical findings and might aid healthcare personnel to more accurately and rapidly triage such patients.

Other methods of quantifying post-radiation exposure effects were suggested in the literature. Biodosimetry quantifies DNA damage using different techniques [37]. Although this approach might provide a more accurate measure of radiation-induced damage, it might be not available in incident locations or logistically difficult to use and get results in real-time for initial triaging, but biodosimetry should be done if applicable [33, 37].

Victims of nuclear accidents should be evaluated thoroughly for symptoms, and detailed history should be taken with an extensive physical examination and appropriate management as described earlier [31, 34].

Hematopoietic supportive care and the role of HCT

The technical aspects of the role of hematopoietic support and HCT [38–44] are given in detail in the supplementary index (S1).

Several supportive measures should be initiated when dealing with patients who develop hematopoietic injury secondary to radiation. Similar to blood diseases and cancers, patients should be transfused with blood products (should be irradiated given immunosuppression) according to local guidelines. Patients with severe pancytopenia might benefit from isolation, and they should receive antibiotics if indicated prophylactically such as in cases of severe neutropenia or if they develop signs of sepsis/febrile neutropenia. Antimicrobial coverage generally should include broad spectrum antibiotics; however, anti-viral and anti-fungals might be needed in patients with prolonged neutropenia [39]. In 2009, WHO tasked a panel of experts to review the best evidence and provide guidance on treating hematopoietic syndrome (HS), the recommendations included using granulocyte colony-stimulating factor (G-CSF) for patients with absolute neutrophil count $< 0.5 \times 10^9$/L (strong recommendation, moderate evidence) and administering erythropoiesis-stimulating agents for severe or prolonged anemia (weak recommendation, low evidence) [38]. Given the current availability, thrombopoietin receptor agonists should also be considered [39]. US RITN website provide guidance regarding G-CSF dosing for filgrastim, pegfilgrastim, and sarograstim [40].

A thorough assessment is crucial in identifying patients with irreversible damage and the possible need for HCT. However, it should be noted that the studies investigating the role of HCT in patients with hematopoietic syndrome are small and limited and some studies suggest worse outcomes after HCT [37, 39–44]. Given the lack of strong evidence, HCT should only be considered after medical therapy failure and should be limited to patients with prolonged BM failure and no concomitant trauma or burns. Once identified, these patients should undergo secondary triaging to centers equipped for HSCT. As in the Fukushima incident, the EBMT and WBMT will work closely with centers mainly in Europe and hospitals in Ukraine to be prepared for any potential nuclear accidents.

The function of the WBMT and its members in secondary triaging of patients with radiation exposure

The WBMT (www.wbmt.org) is a global network of BM transplant and cell therapy related organizations. The members of WBMT are included in Fig. 2 [45]. The WBMT, a non-governmental and not-for-profit organization in official relations to the World Health Organization (WHO) promotes excellence in HCT, stem cell donation, cellular therapy, and accreditation as well as access to HCT worldwide through collaboration of existing international societies encompassing > 1800 transplant centers globally [46]. Its members include the majority of professional regional organizations which deal with HCTs. Details of the member organizations are given in the supplementary index (S2).

The WBMT has established a committee focusing in global emergencies and nuclear accidents. In 2002, one of the WBMT's member organization, the EBMT formed its Nuclear Accident Committee after the 9/11 attack due to increasing concerns of potential terroristic radiation incidents [47, 48]. The committee aims to improve readiness and preparedness by using the society's network of hospitals and qualified hematology-oncology physicians & nurses. The committee has representation from the ten most populated European countries, the WHO Radiation Emergency Medical Preparedness and Assistance Network (REMPAN), IAEA, IRSN, US Radiation Injury Treatment Network (RITN), and German Military Bunderswehr Institute Radiobiology, in addition to governmental representation from European countries and other expert members from outside Europe [47]. Additionally, it serves as a collaborating member of the REMPAN [49]. Memberships and networks were expanded, particularly after the Fukushima incident in 2011. Due to its global reach, WBMT has also formed its Global-Emergencies/Nuclear-Accident (GENA) committee (*co-chairs*, *Ray Powles*, *David M*a, *Shahrukh Hashmi*) to encourage worldwide preparedness, develop international consensus guidelines, and establish collaborations between countries and international institutes, including WHO and IAEA [50].

Worldwide Network for Blood & Marrow Transplantation members

Africa

1. African Blood and Marrow Transplantation group

Australia

1. The Australasian Bone Marrow Transplant Recipient Registry

Europe

1. European Society for Blood and Marrow Transplantation
2. Eurocord
3. The European Federation for Immunogenetics
4. European Leukemia Net
5. The European School for Haematology
6. Joint Accreditation Committee-ISCT

North and South America

1. American Association of Blood Banks
2. American Society for Apheresis
3. American Society for Histocompatibility and Immunogenetics
4. American Society for Transplantation and Cellular Therapy
5. Center for International Blood and Marrow Transplant Research
6. Foundation for the Accreditation of Cellular Therapy
7. Latin America Blood and Marrow Transplantation Group

International and intercontinental

1. Asia Pacific Blood and Marrow Transplantation Group
2. Eastern Mediterranean Blood and Marrow Transplantation Group
3. International Cellular Therapy Coding and Labeling Advisory Group
4. International Society of Blood Transfusion
5. International Society for Cellular Therapy
6. World Marrow Donor Association

Fig. 2 Worldwide Network for Blood and Marrow Transplantation members

Currently, the EBMT has a network of more than 500 hospitals and more than 2000 hematologists. Additionally, the WBMT will coordinate support from the NACs of HCT/cellular therapy societies outside Europe such as ASTCT, APBMT (Asia Pacific Blood and Marrow Transplantation Group), LABMT (Latin America Blood and Marrow Transplantation Group), EMBMT (East Mediterranean Blood and Marrow Transplantation Group) and AFBMT (African Blood and Marrow Transplantation Group) (> 1300 HCT centers). Many of the institutions in Europe might be able to provide help in triaging, providing supportive care, stockpiling of important medications (such as G-CSF, EPO, TPO), storing stem cells; however, a smaller number would be able to provide HCT if needed.

To maintain the standards of transplant centers, the two international accreditation bodies, namely the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE), have established the standards and accreditation systems for BM transplant and BM stem cell collection centers [51–54]. Most JACIE/FACT accredited centers for allogeneic HCT in Europe are the UK, Italy, Germany, and Spain. Localizing the appropriate centers is vital for triaging victims swiftly for further management and possible HCT. Additionally, many centers can provide non-HCT hematopoietic support and this may include centers outside European Union as well.

EBMT role in Fukushima nuclear accident

In March 2011, environmental incident in Japan led to the damage of the power supplying the Fukushima Daiichi nuclear power plant, thus overheating due to the loss of cooling capacity [12]. During the days after the incident, the WBMT and the EBMT nuclear accident committee played a crucial role in alerting its pre-existing network of centers, coordinating the preparedness, and evaluating their resources. More than 400 centers were mobilized/prepared and were committed to helping, whether by receiving patients, looking for unrelated stem cell donors through their own national channels or help in procedures such as stem cell storage. This took place with the help of other international organizations such as the WHO and the US-RITN. Although the health impact was limited, the Fukushima incident was an exercise for the EBMT nuclear accident committee for future incidents [13].

Technical aspects of HCT in radiation victims

The details of technical HCT aspects are given in supplementary index (S3). However, the recommendations are summarized in Fig. 3. This document contains new information (in the light of significant advances in the field of HCT) beyond the earlier EBMT document.

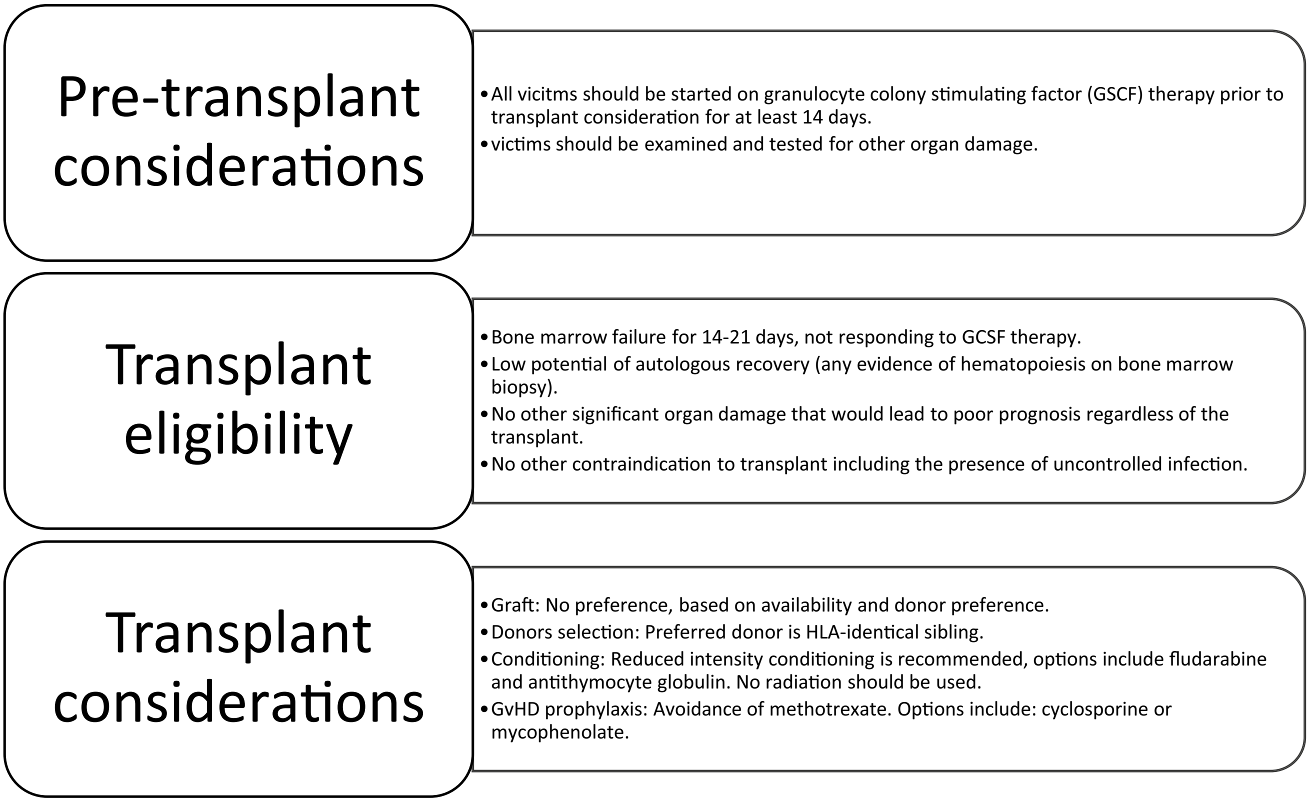

Fig. 3 Summary of transplant related recommendations for radiation victims. Adapted from the WHO consensus meeting and the EBMT pocket guide

Final remarks

Coordination by the WBMT and EBMT is underway to prepare for the worst-case scenario. The roles of HCT societies include but not limited to:

- The coordination and communication with other international and regional organizations including but not limited to IAEA, WHO, European Union, RITN, and others.
- Facilitate the dissemination of treatment protocols to impacted institutions.
- Provide education using WBMT and EBMT websites by providing webinars and reading material that would be able to aid physicians in primary or secondary triage settings.
- Provide advice in real-time to local physicians for treatment issues and later allogeneic HCT decisions.
- Coordinating HSC collections and storage and guiding such practices.
- Provide the infrastructure for prospective data collection.

The current conflict is another example of nuclear accident risk facing us globally and illustrate the importance of radiation-related injury research as it can advance understanding of best approaches to protect victims from the lethal effects of radiation.

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