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EDITORIAL

Potential for a pluripotent adult stem cell treatment for acute radiation sickness

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Abstract

Accidental radiation exposure and the threat of deliberate radiation exposure have been in the news and are a public health concern. Experience with acute radiation sickness has been gathered from atomic blast survivors of Hiroshima and Nagasaki and from civilian nuclear accidents as well as experience gained during the development of radiation therapy for cancer. This paper reviews the medical treatment reports relevant to acute radiation sickness among the survivors of atomic weapons at Hiroshima and Nagasaki, among the victims of Chernobyl, and the two cases described so far from the Fukushima Dai-Ichi disaster. The data supporting the use of hematopoietic stem cell transplantation and the new efforts to expand stem cell populations *ex vivo* for infusion to treat bone marrow failure are reviewed. Hematopoietic stem cells derived from bone marrow or blood have a broad ability to repair and replace radiation induced damaged blood and immune cell production and may promote blood vessel formation and tissue repair. Additionally, a constituent of bone marrow-derived, adult pluripotent stem cells, very small embryonic like stem cells, are highly resistant to ionizing radiation and appear capable of regenerating radiation damaged tissue including skin, gut and lung.

Key words: Nuclear accident; Acute radiation syndrome; Radiological casualties; Stem cell transplantation; Cellular therapy; Emergency response; Ionizing radiation injury; Hematopoietic rescue; Pluripotent stem cells; Induced pluripotent stem cells; Mesenchymal stem cells; Very small embryonic-like stem cells; Mobilizing agents

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INTRODUCTION

Accidental radiation exposure and the threat of deliberate radiation exposure have been in the news and are a public health concern. This paper will describe the state of the art of stem cell treatment of acute radiation sickness. Acute radiation sickness is defined as "a combination of clinical syndromes occurring in stages during hours to weeks after exposure as injury to various tissues and organs is expressed"[1]. Experience with acute radiation sickness has been gathered from atomic blast survivors of Hiroshima and Nagasaki and from civilian nuclear accidents as well as experience gained during the development of radiation therapy for cancer. Based on these sources, an approximate dose threshold for each target organ (Table 1) and a time course of illness can be estimated (Table 2).

Note that bone marrow failure (infection, hemorrhage) is not the exclusive cause of death. High dose radiation can kill with cerebral edema and enteritis and pneumonitis, independent of infection. These syndromes are unlikely to be treatable with hematopoietic stem cell transplantation. Pluripotent (ability to differentiate into all three germ layers) stem cells with potential to regenerate multiple tissue types would add an important benefit for the treatment of acute radiation syndrome. Very small embryonic-like stem cells that can be obtained from adults in autologous cell-dose quantities offer such an advantage and are discussed in more detail latter in this paper.

The standard of care is described in the United States Armed Forces Radiobiology Research Institute's "Medical Treatment of Radiological Casualties"[2]. There are many complexities to caring for patients after radiation exposure. Patients who have been exposed to an explosion may have life-threatening injury not related to radiation exposure. Patients may be externally or internally contaminated with radioactive particles. Rapid and effective decontamination can prevent serious sequelæ including bone marrow failure. Another complication is radiation induced emesis which can be dehydrating and limit the utility of orally administered countermeasures. Medical countermeasures for radiation exposure can be classified into 3 groups[3]: (1) Radioprotectants prevent radiation damage to cells (e.g., amifostine); (2) Radiation mitigators limit radiation damage (e.g., pentoxifylline); and (3) Radionuclide eliminators enhance excretion of radionuclides (e.g., Prussian Blue).

The aspects of acute radiation sickness for which hematopoietic stem cell transplantation is appropriate is amelioration of bone marrow suppression and immune suppression and tissue damage repair. This would fit the classification of "radiation mitigators" because it limits damage that has already occurred. For purposes of describing the value of hematopoietic stem cell transplantation in acute radiation sickness, patients who received between 2 Gy -10 Gy are recommended to be treated with white blood cell supporting cytokines, either G-CSF (filgrastim, peg-filgrastim) or GM-CSF (sargramostim). Cytokines are unlikely to be clinically useful in most cases where exposure exceeds 4 Gy. Patients for whom CSFs are unsuccessful are candidates for hematopoietic stem cell transplantation. The published data on the success of bone marrow transplantation following non-therapeutic radiation exposure include the experience of 13 Chernobyl victims described in the next section. In total reports from 58 people exposed to radiation in excess of 5 Gy, half of whom had an allogeneic transplant, revealed that only three of 29 patients transplanted were alive at one year post exposure. Deaths occurred due to the development of graft-*vs*-host disease and other complications unique to allogeneic transplant that could be avoided if autologous bone marrow or blood-derived stem cells were collected and stored before the exposure and used in place of allogeneic cells.

CURRENT INFORMATION ON ACCIDENTAL (CIVILIAN) OR DELIBERATE (MILITARY, TERRORISM) RADIATION EXPOSURE

In addition to approximately 20 civilian and 60 military nuclear accidents, there have been 3 major nuclear accidents as of June 2011: Three Mile Island in the United States, Chernobyl in the former Soviet Union and Fukushima Dai-Ichi in Japan. In these accidents, it is very difficult to quantify the amount of radiation released, but some information is available on acute radiation sickness following the accidents. The Three Mile Island accident during which a portion of the nuclear fuel melted down in a TMI-2 reactor, but did not breach the containment walls, occurred on March 28, 1979. The widespread perception of great danger from this accident was based on expert's concern that the containment vessel might explode, widely distributing radioactive material. In fact, the containment vessel maintained integrity. Even though increased radiation levels were detected inside the plant and at least 50 workers were exposed, no acute radiation sickness from this accident has been reported[4,5].

The Chernobyl accident on April 26, 1986 was much more serious with significant public health consequences. The difficulty in verifying documentation and medical records of the government of the Soviet Union makes an assessment of the extent of acute radiation sickness due to the Chernobyl accident impossible to reconstruct. Nevertheless, a comprehensive review of available information was published by the New York Academy of Sciences in November 2009[6]. The lowest estimate of acute mortality from the Chernobyl disaster is 9000 victims[7]. Soviet physicians reported on 13 bone marrow transplantations for acute radiation sickness due to exposure at Chernobyl. Twelve of 13 patients had skin injuries resembling burns from 20%-100% body surface area in addition to decreasing white blood cell counts. Four of 8 patients with non-HLA identical donors received T-cell depleted bone marrow transplants. Only 2 of the transplant recipients survived to the 3 year follow up. The deaths reported were not attributed to prolonged neutropenia/infection or to thrombocytopenia/bleeding. Interestingly, two of the transplant recipients had evidence of transient engraftment with donor cells followed by recovery of autologous bone marrow[8].

Most recently, on March 11, 2011, a magnitude 9 earthquake followed by a tsunami estimated at 14 meters high, destroyed part of TEPCOs Fukushima Dai-ichi nuclear power plant and resulted in several explosions. The International Atomic Energy Commission Briefing disclosed Fukushima prefecture received 1.5 microSv/h on March 31 over a natural background of 0.1 microSv/h[9]. Two workers were reported to have received radiation burns to ankles when wading in contaminated water[10]. These are the only two cases of acute radiation sickness

Table 1 Approximate threshold doses of conventionally fractionated therapeutic radiation for clinically detrimental nonstochastic effects in various tissues

Organ	Injury at 5 yr	Threshold dose (sv)[1]	Irradiation field (area)
Fetus	Death	2	Whole
Bone marrow	Hypoplasia	2	Whole
Ovary	Permanent sterility	2-3	Whole
Lens	Cataract	5	Whole
Testes	Permanent sterility	5-15	Whole
Cartilage, child	Arrested growth	10	Whole
Breast, child	Hypoplasia	10	5 cm^2
Bone, child	Arrested growth	20	10 cm^2
Bone marrow	Hypoplasia, fibrosis	20	Localized
Muscle, child	Hypoplasia	20-30	Whole
Kidney	Nephrosclerosis	23	Whole
Lymph nodes	Atrophy	33-45	-
Liver	Liver failure, ascites	35	Whole
Lung	Pneumonitis, fibrosis	40	Lobe
Heart	Pericarditis, pancarditis	40	Whole
Stomach, small intestine, colon	Ulcer, perforation	45	100 cm^2
Thyroid	Hypothyroidism	45	Whole
Pituitary	Hypopituitarism	45	Whole
Lymphatics	Sclerosis	50	-
Central nervous system (brain)	Necrosis	50	Whole
Spinal cord	Necrosis, transection	50	5 cm^2
Salivary glands	Xerostomia	50	50 cm^2
Cornea	Keratitis	50	Whole
Capillaries	Telangiectasis, fibrosis	50-60	-
Breast, adult	Atrophy, necrosis	> 50	Whole
Rectum	Ulcer, stricture	55	100 cm^2
Skin	Ulcer, severe fibrosis	55	100 cm^2
Eye	Panophthalmitis, hemorrhage	55	Whole
Oral mucosa	Ulcer, severe fibrosis	60	50 cm^2
Esophagus	Ulcer, stricture	60	75 cm^2
Cartilage, adult	Necrosis	60	Whole
Urinary bladder	Ulcer, contracture	60	Whole
Bone, adult	Necrosis, fracture	60	10 cm^2
Ear (inner)	Deafness	> 60	Whole
Adrenal	Hypoadrenalism	> 60	Whole
Vagina	Ulcer, fistula	90	5 cm
Muscle, adult	Atrophy	> 100	Whole
Uterus	Necrosis, perforation	> 100	Whole

[1]Dose causing effect in 1% to 5% of exposed persons. Modified from[49,50].

reported to date. In October 2011, a consensus document was published that includes additional individual case reports from sparsely documented historical civilian accidental exposures with the caveat that information from those reports was insufficient to guide future therapy[11].

From a perspective on military use of nuclear weapons, the acute radiation sickness due to use of atomic weapons on Hiroshima and Nagasaki during World War Two has been reviewed[12]. survey of 1216 survivors of the blast in Hiroshima, sheltered in a building, revealed that 451 died on the first day and 201 died in the succeeding 2 mo, presumably from the hematopoietic component of acute radiation syndrome. Since transplantation had not been developed, there are no data on bone marrow transplant or stem cell treatment of acute radiation sickness after weapons discharge. It is the mortality figures from the Hiroshima and Nagasaki bombs that form the basis of military mathematical models to predict acute radiation sickness following nuclear weapons discharge.

The United States Health and Human Services' Office of Preparedness and Emergency Operations has made public the scenarios being used to prepare the United States. Two of these scenarios (#1 and #11) include nuclear weapons. These scenarios are being used to plan public health resource prioritizations and can be applied to estimate the number of patients who would potentially benefit from hematopoietic stem cell transplantation. National Planning Scenario #1 envisions a 1 KT nuclear detonation[13]. Col. Jarrett published an estimate of a 4 × 3 km oval that would receive 4 Gy from a 1 kT nuclear detonation[1]. Utilizing published population densities (New York City = 4500 people/km^2 and San Francisco = 5400 people/km^2), this area (9.4 km^2) would represent between 42 000 and 50 000 victims. National Planning Scenario #11 envisions a Radioactivity Dispersal Device ("Dirty Bomb") which would produce a "no entry" zone (> 1 Gy exposure) of 500 m in diameter (0.2 km^2). Utilizing the same published population densities as above, this would represent between 900 and 1080 victims[14]. These estimates demonstrate

Table 2 Symptoms, therapy and prognosis of whole body ionizing radiation injury

	0-1 Sv	1-2 Sv	2-6 Sv	6-10 Sv	10-20 Sv	> 50 Sv
Therapeutic needs	None	Observation	Specific treatment	Possible treatment	Palliative	Palliative
Vomiting	None	5%-50%	> 3 Gy, 100%	100%	100%	100%
Time to nausea, vomiting	-	3 h	2 h	1 h	30 min	< 30 min
Main locus of injury	None	Lymphocytes	Bone marrow	Bone marrow	Small bowel	Brain
Symptoms and signs	-	Moderate leukopenia, epilation	Leukopenia, hemorrhage, epilation	Leukopenia, hemorrhage, epilation	Diarrhea, fever, electrolyte imbalance	Ataxia, coma, convulsions
Critical period	-	-	4-6 wk	4-6 wk	5-14 d	1-4 h
Therapy	Re-assurance	Observation	Transfusion of granulocytes, platelets	Transfusion, antibiotics, bone marrow transplantation	Fluids and salts, possible bone marrow transplantation	Palliative
Prognosis	Excellent	Excellent	Guarded	Guarded	Poor	Hopeless
Lethality	None	None	0%–80%	80%-100%	100%	100%
Time of death	-	-	2 mo	1-2 mo	2 wk	1-2 d
Cause of death	-	-	Infection, hemorrhage	Hemorrhage, infection, pneumonitis	Enteritis, infection	Cerebral edema

Modified from[51].

that even "small" events in a crowded environment may create enormous demands on the local medical system, and would probably exceed the capabilities of almost all facilities.

As discussed earlier, currently available treatment for radiation exposures of greater than 1 Gy are palliative. Hematopoietic stem cell transplantation to rescue patients for whom cytokine therapy failed has several limitations. The primary limitation is that the donor pool is limited by the need for at least partial HLA matching. As an example, the United States National Marrow Donor Program reports among 9 million donors, only 650 000 (7%) are African American, making bone marrow matching for African Americans difficult[15]. Similar problems probably exist for other under-represented ethnic groups. Once the hematopoietic transplant has engrafted, there is continuous need for immunosuppression. In addition to the risks of life-threatening infection during titration of immunosuppressant medication, some of these medications have dose limiting acute and chronic toxicity independent of graft-*vs*-host disease[16].

Autologous hematopoietic stem cell treatment would solve the problems of immunosuppression and graft-*vs*-host disease. If people at risk were to receive G-CSF mobilized cells collected prior to exposure than there would be sufficient cells available to prevent the profound cytopenia and immune suppression that follows exposure to 4 Gy or more of radiation. In addition, a small volume of bone marrow (100-200 mL) collected prior to exposure and then expanded *ex vivo* post exposure, may also be sufficient to reconstitute hematopoiesis and immune function. The major concern is whether hematopoietic stem cells capable of re-constituting the bone marrow could be expanded *ex vivo* from 100-200 mL, before bone marrow suppression became life-threatening. Clinical studies using marrow, mobilized blood and cord blood have demonstrated the feasibility of doing so[17-19]. Harvesting hematopoietic stem cells from damaged marrow is being done with complex protocols in cancer treatment. However, there are many reports of protocols failing to mobilize hematopoietic stem cells sufficient for reconstitutive use. For example, fludarabine exposure in adults with follicular lymphoma predicted a poor hematopoietic stem cell harvest evidenced by > 5 d apheresis requirement[20]. In a retrospective analysis of 204 patients, Ford *et al*[21] calculated that platinum based drugs and etoposide exposure were most highly correlated with poor hematopoietic stem cell mobilization as reflected by the absence of CD34+ cells on the first day that the white blood cell count was greater than 500. Stem cell mobilization was reported successful in only 12 of 20 (60%) patients with chronic lymphocytic leukemia[22]. These results suggest that chemotherapy treatment at a minimum impairs hematopoietic stem cell mobilization. In addition, a new study confirms expectations, that age between 65-69 years impairs hematopoietic stem cell mobilization relative to younger patients with the same disease[23]. In contrast, hematopoietic stem cell harvest in children is not limited by mobilization, but by scaling factors in extracorporeal volumes and anticoagulation necessary for the apheresis machine and vascular access for sufficient flow[24]. No reports of hematopoietic stem cell harvest from pregnant women could be found on PubMed search. Ford *et al*[21] did not find any correlation of poor hematopoietic stem cell mobilization with prior radiotherapy which gives these authors hope that victims of acute radiation sickness could have their hematopoietic stem cells successfully harvested. However, radiation damage may result in long term issues such as myelodysplasia and leukemia so use of cells previously stored and not exposed to radiation would appear optimal.

NEW PROCEDURES ON THE HORIZON

New mobilizing agents

New mobilizing agents are being developed to replace the colony stimulating factors. The hematopoietic stem

cell harvesting described above utilized G-CSF (filgrastim or peg-filgrastim) and/or GM-CSF (sargramostim) as mobilizing agents. The newer agent, Mozobil® (perixaflor) was approved in the United States in 2009 and acts by reversibly binding CXCR4 and inhibiting CXCR4/CXCL12 anchoring[25]. Mobilization with Mozobil® (plerixaflor) increased successful 4 d apheresis harvesting from 88% (136/154 patients) with G-CSF (filgrastim)alone to 95% (141/148 patients) with both G-CSF (filgrastim) and Mozobil® (plerixaflor)[25]. Natalizumab is an antibody in development as a mobilizing agent that binds to VCAM-1 and interferes with VCAM-1/VLA-4 anchoring[26].

Though un-glycosylated thrombopoietin combined with G-CSF was effective at mobilizing hematopoietic stem cells, the risk of developing autoimmune thrombocytopenia led to the cessation of development of unglycosylated thrombopoietin[27]. The effect of thrombopoietin agonists on animal models of radiation induced thrombopenia are in progress for the peptide Nplate (romiplostim) and orally dosed small molecule Promecta (eltrombopag) and full length, glycosylated, recombinant human thrombopoietin[27].

Burdelya *et al*[28] reported mouse radio-protective activity from a *Salmonella enterica* flagellin derivative given 1 h after radiation exposure and rhesus monkey protection when given 45 min prior to radiation exposure. Its putative mechanism of action is *via* toll like receptor 5 (TLR5) to nuclear factor-κB (NF-κB) signaling to multiple cytokines including G-CSF. This product is under active development by Cleveland Biolabs, Inc., (Buffalo, NY).

Parathyroid hormone (PTH) appears to mobilize stem cells to peripheral blood in mice with a distinct mechanism from G-CSF[26]. In a Phase 1 study in patients with at least one failed peripheral stem cell harvest attempt, the combination of PTH (teraparitide) for days 1-14 and G-CSF (filgrastim) for days 10-14 prior to apheresis resulted in 9/20 (45%) patients meeting pre-specified mobilization criteria. The authors note that this level of success was also seen in second mobilization attempts with a combination of filgrastim (G-CSF) and sargramostim (GM-CSF). A spontaneous observation study of patients with primary hyperparathyroidism showed CD45+/CD34+/c-kit+ and CD45+/CD34+/CXCR4+ bone marrow progenitor cells were increased relative to matched controls. Interestingly, the primary hyperparathyroidism patients had lower G-CSF dosing than controls, while stem cell factor and erythropoietin were not different between groups[29]. Another spontaneous observation study evaluated hemodialysis patients with varying levels of secondary hypo- and hyper-parathyroidism. In patients with high PTH, circulating hematopoietic stem cells were higher than controls or patients with normal PTH levels. In patients with low PTH, circulating stem cell numbers were lower than patients with normal or elevated PTH[30].

Lastly, α-tocopherol succinate is being explored as a single dose inducer of endogenous G-CSF equivalent to a multiday course of G-CSF (filgrastim)[31].

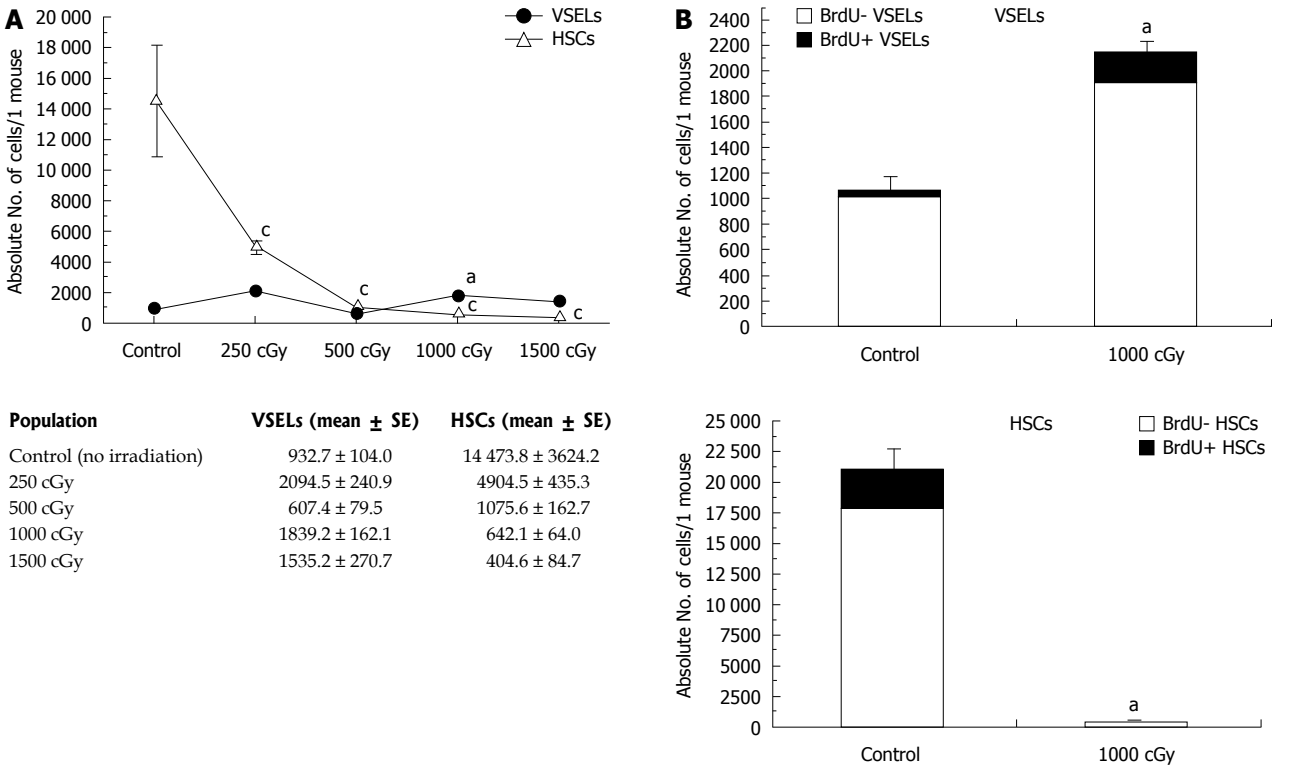
STEM CELL THERAPY

Induced pluripotent stem cells

Another source of cells to reconstitute radiation damaged bone marrow would be adult induced pluripotent stem cells (iPS). Recent laboratory work shows that fibroblasts can be induced to become pluripotent stem cells without using retroviruses, only using mRNA for key transforming factors[32]. Human iPS maintain a flat colony morphology in the laboratory when maintained with basic Fibroblast Growth Factor. Induction of iPS into hematopoietic stem cells covering all three lineages (myelopoietic, erythropoietic and thrombopoietic) has not yet been described. Current laboratory confirmation of pluripotency is the ability of iPS to form teratomas *in vitro* and *in vivo*. Though this is a large potential clinical problem, progress continues to be made and a recent report describes reprogramming skin fibroblasts from a patient with thalassemia (single gene mutation)[33]. Laboratory size colonies appeared in 3 wk following transfection with an engineered retrovirus and were induced to form "hemaglobinized" (HbF producing) colonies in another 2 wk using specially prepared growth media. No description of resulting myeloid or thrombopoietic cells were offered[33]. In addition, the "retro-differentiation" process currently requires approximately 100 adult cells to create 1 induced pluripotent stem cell (1% efficient) and the cells so produced exhibit early senescence[34]. Recently Zhao *et al*[35] have shown that iPS can be rejected due to abnormal gene expression in some iPS cells which can induce a T-cell- dependent immune response. These authors recommend that the immunogenicity of autologous cells should be carefully evaluated before these cells are considered for therapeutic purposes. So as of this writing, iPS are not on the near-horizon for clinical use in acute radiation sickness. Barriers that will need to be overcome to use iPS to treat acute radiation sickness include: production of all three bone marrow lineages from iPS; managing the risk of using oncogene sequences for induction or the identification of alternate induction techniques; improving the speed of hematopoietic stem cell production to a timeframe consistent with rescuing the patient from bone marrow failure; eliminating the risk of rejection; and scaling up production for mass casualties.

Mesenchymal stem cells

A commercial product of human mesenchymal stem cells (MSC) prepared from multiple bone marrow donors (Prochymal®) is being developed for acute Graft-*vs*-Host Disease in bone marrow transplants. Since one lineage of MSC matures into bone marrow stromal cells, MSC have been considered as a supportive treatment for primary engrafting of bone marrow transplants. The initial publication in 2007 that human MSC home to radiation-damaged tissue in mice provided evidence of the potential for restorative therapy outside of the bone marrow[36]. Hu *et al*[37] demonstrated that MSC rescued



Population	VSELs (mean ± SE)	HSCs (mean ± SE)
Control (no irradiation)	932.7 ± 104.0	14 473.8 ± 3624.2
250 cGy	2094.5 ± 240.9	4904.5 ± 435.3
500 cGy	607.4 ± 79.5	1075.6 ± 162.7
1000 cGy	1839.2 ± 162.1	642.1 ± 64.0
1500 cGy	1535.2 ± 270.7	404.6 ± 84.7

Figure 1 Resistance of very small embryonic-like stem cells to γ-radiation. The content of very small embryonic-like stem cells (VSELs) and HSCs was evaluated in murine BM following whole-body irradiation with different doses of g-radiation (250, 500, 1000 and 1500 cGy) when compared to control (no irradiation). A: Absolute numbers of VSELs (Sca-1+/Lin-/CD45-) and HSCs (Sca1+/Lin-/CD45+) in BM after 4 d post-irradiation. The table presents mean numbers of VSELs and HSCs per mouse (mean ± SE). $^{a}P < 0.05$ *vs* control (VSELs); $^{c}P < 0.05$ *vs* control (HSCs); B: Absolute numbers of VSELs and HSCs incorporating BrdU following whole-body irradiation. Data are presented as mean absolute numbers of VSELs and HSCs per mouse (mean ± SE) (From Ref.[43], with permission). $^{a}P < 0.05$ *vs* Control.

fatally irradiated mice. Lange *et al*[38] extended the findings to show that MSCs effect rescue in fatally irradiated mice by anti-inflammatory and "hematopoietic stem cell niche modulating" effects such that endogenous hematopoiesis recovers. Thus, it is possible that MSCs may indeed have a beneficial effect in acute radiation sickness, however it is credible that this effect is due to paracrine, trophic and endogenous stem cell recruitment, rather than a regenerative capability. As the work of Heider *et al*[39] would suggest, bone marrow derived pluripotent stem cells give rise to MSCs and thus are supportive of the role of MSCs in hematopoiesis, but MSCs themselves are not regenerative.

In this setting, Osiris Therapeutics and Genzyme Corporation are collaborating to develop Prochymal® for the treatment of acute radiation sickness. Current clinical trials in steroid refractory graft-*vs*-host disease, where patients have received significant radiation exposure to treat their underlying disease, will provide a human model on which to base animal studies of Acute radiation sickness[40].

Myeloid progenitor cell product

Though not a stem cell product, CLT008, being developed by Cellerant Therapeutics (San Carlos, CA), is a multi-person sourced human cell population derived from donor bone marrow. This product is reported to have capability to mature into monocytes, neutrophils and red blood cells. Though it does not have the potential to mature into T and B lymphocytes, it is being considered as a temporary therapy until the host marrow recovers[41].

Very small embryonic-like cells

Very small embryonic-like cells (VSELs) are pluripotent and present in many tissues and circulate in peripheral blood. The properties and therapeutic potentials of VSELs have been recently reviewed[42]. VSELs can differentiate into multiple cell types *in vitro* and in mice[43]. Kassmer *et al*[44] recently reported that bone marrow derived stem cells that were not hematopoietic were able to differentiate into type 2 pneumocytes in fatally irradiated mice. These small bone marrow cells were reported to be identical to VSELs (personal communication, DS Krause, 2010). VSELs have been documented to be present during routine bone marrow or hematopoietic stem cell harvesting[45]. Ratajczak and colleagues report that in addition to hematopoietic stem cells, VSELs are mobilized during burn injury[46]. This adds important information to the mobilization of VSELs during acute myocardial infarct and stroke in humans[47,48]. So it is likely that some spontaneous mobilization of VSELs will be happening during acute radiation sickness. Murine VSELs are highly radiation-resistant relative to a general population of hematopoietic stem cells, tolerating 1 Gy of γ radiation

and retaining *ex vivo* pluripotent differentiating activity (Figure 1)[43]. Also important is that the *ex vivo* expansion of VSELs requires only 5-10 d in culture[43]. Barriers that will need to be overcome to use VSELs to treat acute radiation sickness include: confirming radio-resistant characteristics of VSELs in humans; confirming that VSEL expansion using growth media doesn't activate oncogenes; and scaling up production for mass casualties.

CONCLUSION

Bone Marrow reconstitution as a partial treatment for acute radiation sickness has developed significantly since bone marrow transplantation was utilized for Chernobyl disaster victims in 1986. Use of autologous bone marrow or mobilized and harvested hematopoietic stem cells should eliminate the risk of graft-*vs*-host disease. The potential of autologous sourced stem cells is being evaluated now. Autologous cell sources include induced hematopoietic stem cells, induced pluripotent stem cells from adult differentiated tissue, MSC from bone marrow, myeloid progenitor cells from bone marrow, and VSEL stem cells from peripheral blood. Autologous human VSELs are emerging as fully functional stem cells that not only have wide-ranging regenerative competence, but have the critically important attribute of radiation resistance. The ultimate goal will be utilizing autologous, expanded stem cell infusions that would reconstitute many of the tissues damaged by radiation exposure.

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