FOLIA HISTOCHEMICA ET CYTOBIOLOGICA
Vol. 43, No. 4, 2005
pp. 223-227

Review article

Which place for stem cell therapy in the treatment of acute radiation syndrome?

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Abstract: Radiation-induced (RI) tissue injuries can be caused by radiation therapy, nuclear accidents or radiological terrorism. Notwithstanding the complexity of RI pathophysiology, there are some effective approaches to treatment of both acute and chronic radiation damages. Cytokine therapy is the main strategy capable of preventing or reducing the acute radiation syndrome (ARS), and hematopoietic growth factors (GF) are particularly effective in mitigating bone marrow (BM) aplasia and stimulating hematopoietic recovery. However, first, as a consequence of RI stem and progenitor cell death, use of cytokines should be restricted to a range of intermediate radiation doses (3 to 7 Gy total body irradiation). Second, ARS is a global illness that requires treatment of damages to other tissues (epithelial, endothelial, glial, *etc.*), which could be achieved using pleiotropic or tissue-specific cytokines. Stem cell therapy (SCT) is a promising approach developed in the laboratory that could expand the ability to treat severe radiation injuries. Allogeneic hematopoietic stem cell transplantation (BM, mobilized peripheral blood and cord blood) transplantation has been used in radiation casualties with variable success due to limiting toxicity related to the degree of graft histocompatibility and combined injuries. *Ex vivo* expansion should be used to augment cord blood graft size and/or promote very immature stem cells. Autologous SCT might also be applied to radiation casualties from residual hematopoietic stem and progenitor cells (HSPC). Stem cell plasticity of different tissues such as liver or skeletal muscle, may also be used as a source of hematopoietic stem cells. Finally, other types of stem cells such as mesenchymal, endothelial stem cells or other tissue committed stem cells (TCSC), could be used for treating damages to nonhematopoietic organs.

Key words: Stem cells - Acute radiation syndrome - Cytokines - Nonhuman primate

Introduction

Acute exposure to high dose of ionizing radiation (IR) leads to acute radiation syndrome (ARS) which is known as a triple neurovascular, hematologic and gastro-intestinal (GI) syndrome. ARS should be considered to be a global illness involving multiple cell communication networks. Indeed, in addition to inducing an early, strong, inflammatory process, high doses of IR induce sequential, deleterious effects responsible for a delayed multiple organ dysfunction syndrome (MODS). Therefore, the medical management of radiation casualties is difficult due to the complexity of RI pathophysiology [10, 21, 35, 42]. Until now, only hematopoietic syndrome can be counteracted by available symptomatic and/or etiologic therapies [32]. The initiation of treatment after radiation exposure is based on presenting clinical signs and symptoms, and rate of decline in absolute lymphocyte count. Within a few days after damage, specific treatment including cytokine therapy is recommended for moderate to severe myelosuppression [16, 42]. However, the higher the radiation dose, the weaker the efficacy of pure hematopoietic GFs, because there are too few residual HSPCs left to respond to cytokine administration. Thus, severe cases of myeloablation require stem cell therapy (SCT).

This rationale can be extended to radiation damages to nonhematopoietic tissues. Injuries caused by intermediate doses of radiation could be cured by means of tissue-specific cytokines, whereas severe damages due to high doses of radiation would require SCT. For example, serious radiological burns have to be treated specifically using skin graft. Endothelial progenitor cell mobilization or transplantation may be another way to promote vascular regeneration [19]. In fact, any therapeutic approach should take into account

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Lecture presented at the Third Annual Meeting of the European Stem Cell Therapeutics Excellence Centre, October 6-9, 2005, Cracow, Poland

the integrated response to radiation by the organism, involving multiple networks of cooperation and regulation.

Current status of therapies for ARS

Supportive care, including blood transfusion, fluids and electrolytes administration, antibiotic and antiviral therapy, remains the basis of medical management [10, 21, 35, 42], in particular in the case of combined injuries (*i.e.*, radiation injury with significant mechanical trauma and/or burns).

The rationale for cytokine therapy is the presence of residual HSPCs in BM areas even after total body irradiation (TBI), due to the constitutive heterogeneity of dose distribution, notably accounted for by the attenuation related to the body's thickness. Hematopoietic GFs have been given to three dozen accidentally irradiated casualties so far [21], but the clinical experience mainly concerns GM-CSF and G-CSF. Consensus treatment guidelines have been lately established in Europe and the USA [10, 16, 21, 32, 42] which recommend that G-CSF be administered soon after exposure until granulocyte and/or platelet (PLT) recovery. Treatment recommendations are summarized in Table 1.

Allogeneic hematopoietic stem cell transplantation using BM, mobilized peripheral blood (PB) and cord blood (CB) cells, has been performed in radiation casualties exhibiting no signs of hematopoietic recovery [11, 33]. However, immune conflicts associated with T cell alloreactivity account for the toxicity of such therapy. Moreover, allogeneic stem cell transplantation is contra-indicated in the case of heavy signs of combined toxicity (burns, GI failure) that lead to poor outcomes [42].

Which place for SCT in the treatment of ARS?

SCT is a large therapeutic strategy [40] including non-manipulated stem cell transplantation (without or with a preliminary step of selection) and *ex vivo* expanded stem and progenitor cell transplantation, the latter being another way of using cytokines. Transient or permanent cell replacement can be sought in accidentally irradiated victims for whom the same challenges have to be taken up as those reported years ago [17].

Treatment of myelosuppression: from stimulation of residual HSPC to hematopoietic tissue replacement

G-CSF and its pegylated form, Peg-filgrastim (designed to exert a prolonged pharmacologic activity [24]) are recommended by the consensus treatment guidelines to stimulate residual hematopoiesis. New approaches to cytokine-based treatment of accidentally irradiated victims have been proposed, particularly to prevent HSPC from apoptosis that has been shown to play a major role in cell death soon after irradiation [5, 13, 20, 26, 36]. Thus, we have developed the concept of "emergency antiapoptotic cytokine therapy" (EACK), based on *in vitro* studies showing the great ability of 4 cytokines in combination (4F), stem cell factor (SCF), FLT3-ligand (FL), thrombopoietin (Tpo) and interleukin-3 (IL-3), to mitigate RI apoptosis at HSPC level and further promote balanced differentiation [13]. We have lately reported the ability of early 4F injection (2 hours + 24 hours after TBI) to rescue mice irradiated at lethal dose 90% from hematopoietic death with persistent benefit regarding long-term survival [20]. In 5 Gy gamma irradiated macaques [15], 4F, given as an early (2 hours) single administration, was shown to counteract HSPC cell death *in vivo*, abrogate the 3 week period of aplasia experienced by untreated controls, and stimulate recovery of all hematopoietic lineages. No apparent impairment of the long-term hematopoietic status and stem cell pool was observed in treated monkeys. Moreover, 4F is still efficient when its single administration is delayed until 48 h after TBI, and partial preservation is observed in 7 Gy irradiated monkeys treated at 2 hours [22]. EACK should be optimized to ensure the survival of individuals exposed to lethal radiation doses, by addition or substitution of different cytokines.

The extent of BM damage is the limiting factor for hematopoietic GF efficacy. Allogeneic stem cell transplantation is made necessary when residual hematopoiesis is too low to provide any sign of hematopoietic recovery in response to cytokine administration [10, 35, 42]. However, whether SCT should aim at providing permanent hematopoietic tissue replacement is very difficult to address at the time of transplantation. Indeed, most of transplanted victims showed transient evidence of donor cell engraftment, followed by autologous hematopoietic recovery [33, 42].

What kind of stem cells can be used for hematopoietic recovery? According to hematologists, BM, PB and CB HSPCs can be used. There have been too few cases of transplantation of PB and CB cells in radiation casualties so far to specify the best source of stem cells, if any, in terms of homing and repopulation potential [17, 29]. More critical is the degree of HLA matching. Syngeneic and geno-identical related donors are preferred. In absence of the former, matched unrelated donors shall be used. The $CD34^+$ cell threshold to be grafted is 2×10^6/kg cells. It is compulsory to avoid the development of graft versus host disease (GVHD). Therefore, in the case of mobilized PB, HSPCs should be depleted of T-cells using $CD34^+$ cell selection. Infusion of allogeneic MSCs may reduce the risk of GVHD [30].

The role of e*x vivo* expansion in this context remains to be determined with respect to stem cell expansion, stem cell phenotype manipulation (*e.g.* upregulation of

Table 1. Recommended doses of cytokines for accidentally irradiated casualties

	Adults	Setting and range of exposure	Precautions of use
Filgrastim or G-CSF	5 µg/kg/d	3 to10 Gy (N <100 casualties; absence of combined injury)	Pregnancy, prothrombotic disorders, significant coronary artery disease, ARDS, acute cerebral ischemia, myeloproliferative and myelodysplastic syndromes
Pegylated-filgrastim or Peg-G-CSF	6 mg per week		
Sargramostim or GM-CSF	250 µg/m^2/d	3 to 7 Gy (mass casualty scenario N>100)	
G-CSF + EPO*	40 000UI/week*	2 to 6 Gy in case of combined lesions (whatever the scenario)	

The different cytokine treatments proposed could be used in the range of 2 and 7 Gy TBI. ARDS: acute respiratory distress syndrome (ARDS).

Table 2. Validated and putative sources of stem cells for the treatment of ARS

	Stem cell sources	Hematopoietic recovery	Non hematopoietic recovery (prevention of MODS)
HSPC	Allogeneic BM, T-cell depleted PB, CB (±eX), SC	+	± (TCSC contamination)
	eX Autologous BM, PB, SC	±	
	Autologous SC from non hematopoietic tissues (liver, muscle...) ± eX	±	
Specialized and multipotent SC	MSC	+ (support in co- transplantation with auto/allo HSPC)	±
	Endothelial progenitor cells		±
	TCSC		±

HSPC: hematopoietic stem and progenitor cell; MODS: multi-organ dysfunction syndrome; SC : stem cells ; MSC: mesenchymal stem cell; TCSC : tissue-committed stem cells, eX: *ex vivo* expansion.

cell adhesion molecules or chemokine receptors) or progenitor cell proliferation. As for CB, *ex vivo* manipulation is a prerequisite for transplantation in adults. Based on clinical trials in cancer patients receiving an autologous graft [38], co-transplantation of both non manipulated and *ex vivo* expanded HSPCs from the same allogeneic donor, may be beneficial to prevent the period of pancytopenia while ensuring long-term recovery.

Autologous SCT might also be applied to radiation casualties provided a sufficient amount of residual HSPCs is collected after irradiation and these cells are then efficiently expanded *ex vivo*. Different laboratories have performed feasibility studies in animal models [3, 4]. In this context, co-cultures on stromal or endothelial cell layers have been shown to provide a definitive advantage to the graft [6, 8]. We have also shown that co-culture of irradiated baboon CD34$^+$ cells on MSCs and co-transplantation to lethally irradiated recipients led to increased PLT recovery [14]. Nevertheless, this strategy remains questionable due the small size of produced grafts.

TCSC [28] or totipotent stem cells have been described as new sources of stem cells [31]. In particular, hematopoietic potential of the liver and the skeletal muscle has been evaluated, mainly to a purpose of autologous transplantation in oncological settings [9, 25]. Different methodologies have been pursued involving unselected mononuclear cells (MNC), CD34+ cells or "side population" (SP) cells. In fact, hematopoietic capacity of adult human skeletal muscle appears to be negligible [1, 18]. On the contrary, transplantable hematopoietic stem cells would reside in human fetal and adult liver [27, 41]. Our team has lately shown that transplantation of autologous hepatic MNCs could contribute to granulopoietic reconstitution in a nonhuman primate model of myelosuppression [23]. Ongoing studies will address the relevance and effectiveness of such stem cell sources for treatment of ARS.

Treatment of nonhematopoietic damages

IR induce damage to nonhematopoietic tissues (epithelial, endothelial, glial, *etc.*), which strongly suggests that therapeutics could include tissue-specific and pleiotropic cytokines such as erythropoietin (Epo) and keratinocyte growth factor (KGF) in addition to already cited hematopoietic GFs, to ensure tissue damage repair and mitigate the inflammatory processes. These cytokines should be administered soon after damage in an attempt to reduce stem and progenitor cell death. Indeed, not only hematopoietic cells but also cells from non-hematopoietic tissues such as BM stromal cell precursors [34], cryptic epithelial stem cells of the intestinal villi

and endothelial cells of the vasculature [37], undergo apoptosis following irradiation, which confirms the relevance of EACK. Based on high protection observed in lethally irradiated mice, early and short-term administration of Epo and/or KGF combined to antiapoptotic cytokines may result in durable protection of various tissues [FH, MD, unpublished results].

However, the prevention of MODS may require localized or ubiquitous stem and progenitor cells supply. MSCs have been shown to display a certain level of plasticity within the mesoderm and beyond. Teams involved in nonhuman primate research have reported wide but modest biodistribution of MSCs after transplantation in normal and myelosuppressed macaques and baboons [7, 12].

Finally, we assessed the PB $CD34^+$ cell levels after EACK therapy and showed significantly higher and earlier $CD34^+$ cell peak values in treated macaques, sign of greater recovery level, compared to control irradiated animals [15]. One should look for early and delayed endothelial progenitor cell mobilization ($CD34^+$ KDR^+) that might participate in vascular recovery.

Conclusions and perspectives

SCT should be considered in patients severely affected with ARS (i.e. exposed to 7 to 10 Gy) who do not show evidence of hematopoietic recovery, are not affected by severe trauma, burns and GI syndrome, and who have an appropriate donor. Improvement of cytokine therapy by using pleiotropic or tissue-specific cytokines capable of mitigating damages to non hematopoietic organs might broaden the criteria for the selection of radiation casualties for SCT. Use of multipotent or tissue-specific stem cells may be another approach to prevent MODS. In any case, allogeneic grafts highly enriched in stem cells would reduce the risk of immune conflicts.

Gene therapy is another experimental approach. Its goal is to stimulate hematopoiesis through transient or durable overexpression of genes encoding cytokines. This can be achieved by manipulating BM stromal cells using retroviral or adenoviral vector [2, 39]. The safety and efficacy of such an approach have to be validated before going to the clinic.

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Received: June 22, 2005
Accepted: June 25, 2005