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Cellular Therapies for Treatment of Radiation Injury after a Mass Casualty Incident

Carmen Rios[a,1], **Jean-René Jourdain**[b], and **Andrea L. DiCarlo**[a]

[a]Radiation and Nuclear Countermeasures Program (RNCP), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Rockville, Maryland [b]Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-aux-Roses, France

INTRODUCTION

In 2004, the Department of Health and Human Services (HHS) tasked the National Institutes of Health (NIH) and specifically, the National Institute of Allergy and Infectious Diseases (NIAID) with the responsibility of identifying and developing medical countermeasures for use in the event of radiological or nuclear incidents. The NIAID's Radiation and Nuclear Countermeasures Program (RNCP) was established to administer this initiative. A similar mandate from the French Government was enacted with passage of French Order No. 2002-254 of February 22, 2002. This order established the Institut de Radioprotection et de Sûreté Nucléaire (IRSN) as the French Government subject public matter experts in radiation science and its risks.

The RNCP funds basic and advanced research on early and delayed injuries that occur after acute radiation exposure. Although recent U.S. licensure of granulocyte growth factors has been achieved, to date, no cellular therapies are approved for the treatment of radiation injuries, in the context of a mass casualty incident. However, the IRSN, with Percy Hospital in France has been at the forefront in the use of these approaches to treat human radiation injuries resulting from accidental exposures. In July, 2015, the NIAID and IRSN co-sponsored a workshop in Paris, France to discuss development of preclinical radiation injury models, strategies using cellular therapies after a mass casualty incident and possible licensure pathways. This commentary provides a brief overview of the data presented at the meeting, and the key points that were discussed; and correspondingly a meeting report (1) that provides a more complete background and discussion of the workshop is available at http://dx.doi.org/10.1667/RR14810.1.

Human clinical experience

The first known cellular therapy used to treat radiation exposure was in 1958 at the Curie Institute in Paris, France (2). At that time, a victim from an experimental nuclear reactor accident in Vinca, Yugoslavia was treated with a bone marrow transplant (BMT) after being exposed to radiation. The BMT provided a temporary graft; however, no dramatic change in

[1]Address for correspondence: DAIT, NIAID, NIH 5601 Fishers Lane, Room 7A65; Rockville, MD 20852; riosci@niaid.nih.gov.

patient outcome was observed, presumably because the therapy was delivered too late after the incident (first administered at day 28 postirradiation). Following the Chernobyl accident, 13 patients received cell transplants with a 10% survival rate (3). In an evaluation of 58 victims of high doses of radiation (total-body dose >5 Gy), where 29 patients received stem cell transplants; there did not appear to be a significant survival benefit, except in cases where the damage was limited to the hematopoietic system (4). In 1999, following a criticality accident in Tokai-Mura, Japan, two victims who received high-dose exposures (estimated 5.4 Gy of neutrons/8.5 Gy gamma rays for Patient A and 2.9 Gy neutrons/4.5 Gy gamma rays for Patient B) were treated with hematopoietic stem cell transplants (5). The transplants were successful in both patients; however, they later died from multiple organ failure (6). Taking these diverse outcomes into account, a series of meetings and an international consensus conference were convened in 2009, to evaluate the potential use of bone marrow transplants for acute radiation exposures. The final recommendation of the assembled subject matter experts was to administer transplants only in cases where there are no signs of endogenous bone marrow recovery. Further, cytokines should be used as the first line of therapy — based on accidental human exposures where only growth factors were administered and resulted in reasonable success (7). Previous clinical use of cellular therapies for other injuries, including skin, also suggests the potential use of these approaches for treating radiation exposures that do not involve a hematopoietic component. For example, an accident victim in Senegal in 2007 received local mesenchymal stem cell (MSC) injections for cutaneous radiation injury. The treatment, carried out at the same time as surgery to excise the lesion, led to complete healing of the skin, reduction in pain and improved function (8). Successful outcomes seen with stem cell transplants to treat cancer and other diseases can also be leveraged to understand the most judicious use of these treatments for radiation injuries.

Mass casualty logistics

In the immediate aftermath of an incident, there will be limited resources and a narrow window of time in which to initiate therapy. Administering any cellular therapy will be a significant hurdle, especially if a matching donor is needed. One way to overcome this is to use cells that are either immunologically-privileged or protected due to the myelosuppression that occurs after irradiation — the body is essentially unable to reject the cells in the short-term. Autologous transplants are also challenging, as there is the possibility that an individual’s own cells may have been irradiated along with the organs/tissues that need repair, possibly rendering the transplanted cells less effective. Nonetheless, radiation exposures will most likely be heterogeneous, making it possible to collect cells for transplants from tissues that were spared from exposure.

Other challenges involved in the use of cellular therapies in a mass casualty setting are the probability that treatments will require intravenous administration by knowledgeable health care staff, and that cellular therapies could require liquid nitrogen for storage and/or equipment and supplies to thaw and prepare the cells. These factors will likely limit the use of certain cellular therapies to a definitive care, hospital setting.

Regulatory licensure considerations

A special licensure pathway — the "Animal Rule" — must be followed for a cellular therapy for mass casualty use to be evaluated by the Center for Biologics Evaluation and Research (CBER) within the U.S. Food and Drug Administration (FDA). The Animal Rule is applied when a product is developed to treat or prevent life-threatening conditions caused by "exposure to lethal or permanently disabling toxic substances, when efficacy studies in humans ethically cannot be conducted." The FDA Animal Rule document (21 CFR 314.500 for drugs and 21 CFR 601.90 for biologics), and guidance issued in 2015 (9), provide information on the data from pivotal animal studies that must be obtained before approval can be considered. The FDA has also published other guidance documents specific to cellular therapies (10–12). Scientists at the FDA/CBER oversee licensure requests and are also participants in a U.S.-based MSC research consortium, with the goal of assuring safety and efficacy of stem cell-based products (13). Similarly, the European Union (EU) has a regulatory framework to approve new cellular therapies for use in human populations (14). Objectives of the EU's advanced therapy medicinal product (ATMP) regulations are to promote market access of cellular products and ensure protection of patients. The Committee for Advanced Therapies (CAT), established by the European Medicines Agency (EMA) in 2007 has as its role to define cellular products that could be used clinically. The CAT's responsibilities also include assuring the safety and quality of ATMPs and monitoring recent research developments.

In the U.S. and Europe, treatment of humans exposed to radiation in a public health emergency with a cell product that is not approved for such use would be considered "investigational use" and would require authorization for emergency use from the appropriate regulatory authority (FDA in the US; European Medicines Agency (EMA) in Europe). The FDA authorization would be accomplished through either an investigational new drug application (IND) or an Emergency Use Authorization (EUA), while an ATMP approval for a specific application from the EMA would be needed in Europe (14–16).

Diversity of cellular therapies

Stem cells can be derived from different biological sources, including the bone marrow and vasculature, adipose tissue, placenta, amniotic fluid, cord blood and gingival/dental tissue. They can also be fetal-derived or created using induced pluripotent stem cell technologies. As presented at the meeting (and referenced in the full meeting report), many of these cellular therapies have been successful in treating preclinical animal models for radiation-induced injuries in different organ systems:

- *Cutaneous*. IRSN researchers have shown efficacy of cellular therapies in human patients with radiation cutaneous injuries from industrial accidents (17, 18), and in preclinical models of radiation-induced skin injury to suppress inflammation and reduce fibrosis and scarring (19–22).
- *Hematopoietic*. In addition to human clinical experiences provided above, in preclinical models, transplantation of hematopoietic stem cells, and administration of endothelial cells has been shown to mitigate bone marrow injuries. Replacement of lost cells minimizes further tissue damage, restores

hematopoiesis after lethal total-body irradiation and accelerates organ regeneration (23, 24).

- *Lung*. Studies in animal models for lung disease suggest a benefit of administration of cellular therapies and represent a potential treatment for radiation injury (25, 26). Onset of lung injury is delayed; therefore, it may be possible to initiate therapy at times long after radiation exposure and still see benefit.
- *Central Nervous System (CNS)*. Radiation exposure can cause acute and long-term effects in the CNS, such as cognitive dysfunction. Several studies have shown that the administration of neuronal stem cells or microvesicles to cranially irradiated animals leads to improved performance on behavioral tasks and reduced inflammation (27, 28).
- *Gastrointestinal (GI).* Studies show that cellular therapies restore the intestinal stem cell niche after irradiation (29), and that administration of MSCs can improve survival, restore intestinal structure and function and increase epithelial cell proliferation (30).

In response to the successful use of cellular therapies in preclinical models of radiation injury, several commercial interests are exploring cellular therapies for radiation mass casualty use. For example, Cellerant Therapeutics' lead product, CLT-008, is a myeloid progenitor cellular therapy that is being developed for several indications, including acute radiation syndrome (ARS). When administered up to six days postirradiation, the product dramatically improves survival after radiation doses that induce both the hematopoietic and GI sub-syndromes of ARS (31). Another company, Pluristem Therapeutics, Inc. is developing "off-the-shelf" cells derived from human placenta. Their PLX-R18 cells, under development for transplant indications and ARS, have been shown to improve survival in mice when administered after radiation injury (32).

Importance of animal models and human data

As described above, animal models allow for evaluation of cellular therapies in a physiological context. In the animal, it is possible to assess potential variables with radiation exposures, combinations of injury/diseases, mechanisms of action of a therapy and efficacy. Although human data are normally preferred, available sources of human samples often have confounders. Cancer patients, for example, receive focused and localized exposures (whereas heterogeneous exposure is expected in a radiation incident), and concomitant chemotherapy and co-morbidities can complicate analysis. Nonetheless, human studies conducted for other indications could be leveraged to provide supportive information for the radiation indication.

Factors that impact efficacy of cellular therapies

Situations that can interfere with the successful use of cellular therapies include donor age (33), co-morbidities (34) and details of cell harvesting (e.g., when they were isolated, time in culture, passage number and if the cells were frozen and then thawed). This last point is critical; cryopreserved cells require more culture time to return to their prefreeze metabolic

state, and if immediately infused, may not have sufficient time to recover potency. Culturing cryopreserved cells after thawing; however, has been shown to rescue function (35). While freeze-thawed cells for both preclinical and clinical use are appropriate, extra care must be taken to ensure that findings are similar to those obtained with fresh cells.

As shown here, much work has been done to demonstrate the potential of cellular therapies for use in a radiological or nuclear incident. Nevertheless, many questions remain as to the most appropriate approach, in terms of cell source, cell type and organ system to target for treatment. Logistics in a mass casualty scenario is a continuing topic of concern that will require strategic planning for successful implementation. Provision of future funding in this scientific area would allow for these issues to be addressed, and for the establishment of cellular therapies as optimum, life-saving approaches for use in victims suffering from acute and delayed radiation injuries.

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