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FRONTIER

Fifteen years of preclinical and clinical experiences about biotherapy treatment of lesions induced by accidental irradiation and radiotherapy

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Abstract

High dose radiation exposures involving medical treatments or accidental irradiation may lead to extended damage to the irradiated tissue. Alleviation or even eradication of irradiation induced adverse events is therefore crucial. Because developments in cell therapy have brought some hope for the treatment of tissues damages induced by irradiation, the Institute for Radiation and Nuclear Safety contributed to establish the clinical guidelines for the management of accidentally irradiated victims and to provide the best supportive care to patients all over the world. In the past 15 years, we contributed to develop and test cell therapy for protection against radiation side effects in several animal

Biography

Alain Chapel, PhD, scientific investigator at Institute of Nuclear Safety and Radioprotection (IRSN), is team leader in Laboratory of Radiopathologie and Experimental therapies. Since 20 years, he developed gene and cell therapy gene of non-human primate, immune-tolerant mice and rats to protect against side effects of radiation. He has developed representative experimental models of SAI to investigate the effect of radiation on both the radiosensitive hematopoietic cells and their bone marrow microenvironment. He collaborates with clinicians to develop new strategies for treatment of patients after radiation accidents or radiotherapy overexposures. In compassional trials, he has participated to the first to establishment a proof of concept of therapeutic efficacy of mesenchymal stem cells (MSCs) for the treatment of hematopoietic deficit, radiodermatitis and the over dosages of radiotherapy. In collaboration with Saint-Antoine Hospital (Paris, France), he has contributed to the first reported correction of deficient hematopoiesis in patients (graft failure and Aplastic Anemia) thanks to the intravenous injection of MSCs which restored bone marrow micro-environment, mandatory to sustain hematopoiesis after total body irradiation. Currently his work focuses on the development of radio-induced bone marrow aplasia using human hematopoietic stem cell derived from human IPS. He is member of various learned national and international societies: European Bone Marrow Transplantation Group (EBMT), American Society for Hematology; International Society of Stem Cell Research, member of Société Francaise de Greffe moelle et de thérapie cellulaire. He is associate editor of 5 international reviews: *World Journal of Stem Cells*, *World Journal of Gastrointestinal Surgery*, *World Journal of Radiology*, *The Open Gene Therapy Journal*, *Journal of Clinical Rehabilitative Tissue Engineering Research*. He has participated to scientific organization of international conference of the European group for Blood and Marrow Transplantation, EBMT Paris 2011.

models, and we proposed mechanisms to explain the benefit brought by this new therapeutic approach. We established the proof of concept that mesenchymal stem cells (MSCs) migrate to damaged tissues in the nonobese diabetic/severe combined immunodeficiency immunotolerant mice model and in non-human primate after radiation exposure. We showed that the intravenous injection of MSCs sustains hematopoiesis after total body irradiation, improves wound healing after radiodermatitis and protects gut function from irradiation damages. Thanks to a tight collaboration with clinicians from several French hospitals, we report successful treatments of therapeutic/accidental radiation damages in several victims with MSC infusions for hematopoiesis correction, radio-induced burns, gastrointestinal disorders and protection homeostatic functions of gut management after radio-therapy.

Key words: Mesenchymal stem cells; Radiotherapy; Cell therapy; Stem cells; Healthy tissue; Tumor; Radiation

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INTRODUCTION

Radiation therapy, the primary treatment of many cancers, induces lesions to the healthy tissues on the short and long term. About 1.5 million patients undergo external radiotherapy each year in Europe. Acute adverse effects are present in 80% of them including late adverse effects in 5%-10%. About 90000 patients a year receive abdominal/pelvic radiation therapy. Five percent to 10% of patients develop late side effects, the more severe pathologies being hemorrhages, fistula, and fibro-necrosis, all recognized as "pelvic radiation diseases". Infrequently, as in the Epinal accident (with Recto-vesical fistulas) in 2005 these complications can lead to death. Alleviation or even eradication of radiation induced adverse events is therefore crucial. Accidental radiation exposure, such as seen during the last events at Fukushima in 2011, reminded and emphasized that the "zero risk" level in nuclear industries does not exist, and that research and development of new therapies should be absolutely reinforced. Novel therapies are needed to answer the major risk of radiation crises, in part by proposing efficient medical counter measures in cases of external exposure typical for a major nuclear accident[1,2].

PREVENTION AND TREATMENT OF IRRADIATION VICTIMS

The Institute for Radiation and Nuclear Safety is the French National Agency responsible for prevention and treatment of radiation victims. Institute manages a reference network to support and treat patients with radiation induced lesions resulting from radiation therapy or accidental radiation exposure. This platform is based on the development of innovative clinical protocols using mesenchymal stem cells (MSCs) from human bone marrow. It will also explore other sources of stem cells such as pluripotent adult stem cells (IPS) to develop and offer new protocols.

Research and clinical platform

This research and clinical platform is a network composed of different research groups to allow for a multidisciplinary approach. These research groups include research teams from the University Pierre and Marie Curie and radiobiology experts collaborating with the UPMC (IRSN/Department of Human Radioprotection-DRPH), as well as clinical research teams at Saint Antoine Hospital (Department of Clinical Hematology) and Henri Mondor Hospital [Parisian Section of the French Institute of Blood (EFS IdF), Department of Cell Therapy] part of the Parisian Health and Hospital Network (APHP).

This network gathers complementary expertise for the biotherapeutic treatment of radiation therapy side effects and accidental radiation exposure. This therapeutic platform for irradiated patients handles upstream investigations to clinical protocol trials and benefits from the following competences: (1) fundamental research on pluri- and multi-potent cells; and (2) research and development: production of innovative cell therapy products, and R and D of cell therapy products and the creation of a stem cell (IPS) bank for grafting purposes; preclinical animal trials of therapeutic efficiency and study of tissue lesions repair mechanisms following stem cell transplantations, support, trials and intervention protocols, renowned for its expertise in the treatment of overdosed radiation therapy patients, *i.e.*, Epinal cases) and Blood Center Transfusion of Army (CTSA, Percy Hospital, Clamart, France) renowned for its expertise in the treatment of radiodermatitis. Since this partnership has been established several accidents have occurred, in Belgium, Chile, Peru, Japan and also in France at Epinal where a first cohort of 22 patients with prostate cancer has received a dose of irradiation 20% higher on irradiation fields 20% larger than initially planned[3,4].

Preclinical treatment of radio-induced damages

We have proposed innovative cell therapies for treatment of patients. We have developed, tested and proven that using of cell therapy allows the regenerate damaged tissue after radiation therapy. We established that MSCs migrate to damaged tissues in immunotolerant mice model and in non-human primates after radiation exposure[5-8]. In immunotolerant mice, we showed that the intravenous injection of MSCs sustains hematopoiesis after total body irradiation[6], improves wound healing after radio

dermatitis[9,10] and protects gut function[11]. MSCs restore gut functions after radiation, through regulation of endogenous epithelial cell homeostasis[12]. We showed that MSC treatment increases and accelerates the recovery of the small intestine with reversible alterations and extends the life of animals developing irreversible gastrointestinal alterations. Histopathological evaluations provided initial insight into the cellular targets of therapy. MSCs effects are a consequence of their ability to enhance or maintain the re-epithelization process of small intestinal epithelium. To our knowledge, this is the first demonstration that MSC therapeutic effects on small intestinal damage lead to the re-establishment of cellular homeostasis by both increasing endogenous proliferation processes and inhibiting apoptosis of radiation induced intestinal epithelial cells. Furthermore, we demonstrate that MSCs have distant sustained effects[13]. We found that the MSCs regenerated the small intestinal epithelium, which in turn restored the enterohepatic recirculation pathway initially damaged by irradiation. The consequence was a sustained hepatic protection without engraftment of MSCs in liver. Another mechanism that should be considered is the role of cytokines and growth factors released by the MSCs that are homing to other organs, the paracrine biofactors in MSCs-mediated enhanced wound healing. We previously reported that MSCs act mainly by immunomodulation mechanisms[14-19]. Cell therapy combining different sources of adult stem cells is under investigation and is being tested in preclinical models of radio induced damage[20,21]. In parallel, we started analyzing potential side effects of MSCs injections[22].

TREATMENTS OF THERAPEUTIC/ ACCIDENTAL RADIATION DAMAGES

Thanks to a tight collaboration with clinicians, to the best of our knowledge our group is the first to report successful treatments of therapeutic/accidental radiation damages in several victims with MSCs injections in: (1) radio-induced burns: cutaneous reactions are major actors in radiation accidents and a limitation for radiotherapy. In collaboration with Percy hospital (Clamart, France), we have shown for the first time the efficiency of MSCs therapy in seven patients with acute cutaneous and muscle damages following accidental irradiation delivered at doses and to fields higher than initially planned[23]; (2) gastrointestinal disorder management: we are the first to treat patients over irradiated in Epinal with infusion of MSCs, following a specific mission form the French ministry of health. In 2008, three overdosed Epinal patients presenting serious intestinal radiation induced lesions, compassionately received MSCs treatment. For all three patients, the systematic administration of MSCs was well tolerated; efficient analgesic and anti-inflammatory effects as well as hemorrhage reduction were observed. A fourth patient was successfully treated in 2012[24]. Compassionate trials demonstrated the feasibility of cell therapy by MSCs for patients overdosed during radiation therapy of prostate cancer in Epinal Medical Center. A new protocol will be performed in 2013 for the treatment of late severe damages of abdominal radiotherapy. Furthermore, in collaboration with APHP and UPMC, the IRSN is currently participating in a surveillance protocol of a cohort of patients overdosed during radiation therapy for prostate cancer at Epinal Medical Center; and (3) hematopoiesis correction: in collaboration with Saint-Antoine Hospital (Paris, France), we are the first to report the hematopoiesis recovery in two patients with Bone Marrow failure (graft failure post grafting and Aplastic Anemia) after intravenous injection of MSCs which restored the BM micro-environment, mandatory to sustain hematopoiesis after total body irradiation[15,25]. In case of severe accidental radiation exposure, the primary life-threatening symptom that can occur is medullar aplasia. The field of stem cell research has been profoundly impacted for the long term by the recent technology of adult cells reprogramming. UMRS-938 and IRSN are developing an alternative, innovative therapy to treat this hematologic syndrome by revisiting allogeneic transplantation, thus far inconceivable for accidentally irradiated individuals. The innovation is to generate stem cells from IPS originating from healthy, extra-hematopoietic tissues preserved from the radiations to restore a functional hematopoiesis in these patients.

CONCLUSION

Radiotherapy is associated with a high incidence of undesirable acute and/or chronic complications that can affect the patient's quality of life and/or may be life threatening. The lack of curative treatment at present and the potential severity for the disorder highlight the importance of novel and effective therapeutic strategies after radiation exposure. Stem cells can be used to treat toxic side effects induced by irradiation on healthy tissue. As demonstrated in a preclinical model, MSCs may offer a novel strategy to treat radiation diseases. There is interest in using these adult stem cells in critical illness, however, the safety profile of these cells is not well known. Lessons from clinical trials must be taken into account; since the first reported trial in 1995, cultured MSCs have been used in 125 registered clinical trials. In the past 15 years, we contributed to develop and test cell therapy for protection against radiation side effects in several animal models. We report successful treatments of therapeutic/accidental radiation damages in several victims with MSCs infusions for hematopoiesis correction, radio-induced burns and gastrointestinal disorder management after radio-therapy. Concerning gastrointestinal disorder, new protocol will be proposed for the treatment of late severe damages of abdominal radiotherapy. With regard the hematopoiesis, we will generate stem cells from IPS originating from healthy extra-hematopoietic tissues to restore a functional hematopoiesis in patients with acute hematopoietic syndrome.

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