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
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 mouse 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 radiotherapy.

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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 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 pluripotent 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[6].

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[7-8]. In immunotolerant mice, we showed that the intravenous injection of MSCs sustains hematopoiesis after total body irradiation[4], improves wound healing after radio
dermatitis[9,10] and protects gut function[11]. MSCs restore
gut functions after radiation, through regulation of en-
dogenous epithelial cell homeostasis[12,13]. 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 epithe-
lum. To our knowledge, this is the first demonstration
that MSC therapeutic effects on small intestinal dam-
age 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 previ-
ously reported that MSCs act mainly by immunomodula-
tion 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 dam-
age[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 success-
ful treatments of therapeutic/accidental radiation dam-
ages 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 min-
istry 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]. Compassion-
ate 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 col-
laboration 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 hematopoie-
sis recovery in two patients with Bone Marrow failure
(grant 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[15,28]. In case of severe ac-
cidental 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 re-
programming. 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 unde-
sirable 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 poten-
tial 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 con-
tributed 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 ab-
dominal radiotherapy. With regard the hematopoiesis, we
will generate stem cells from IPS originating from healthy
extra-hematopoietic tissues to restore a functional hema-
topoiesis in patients with acute hematopoietic syndrome.
REFERENCES

1 Thiery D, Bertho JM, Chapel A, Gourmelon P. Cell therapy for the treatment of accidental radiation overexposure. BJH Suppl 2005; 27: 175-179 [PMID: 15975892 DOI: 10.1259/ bjhar2005_306]

2 Benderitter M, Gourmelon P, Bey E, Chapel A, Clairand I, Prat M, Lataillé J. New emerging concepts in the medical management of local radiation injury. Health Phys 2010; 98: 851-857 [PMID: 20445393 DOI: 10.1097/ HP.0b013e3181979a74]

3 Voswinkel J, Chapel A. [Mesenchymal stem cells and rheumatism. State of the art]. Z Rheumatol 2012; 71: 619-623 [PMID: 22922552 DOI: 10.1007/s00277-011-0890-z]

4 Chapel A. Mesenchymal stromal cell therapy to repair radiation-induced intestinal damage: implications for treatment of abdominopelvic malignancy. Cytotherapy 2012; 14: 1157-1158 [PMID: 23066783 DOI: 10.3109/14653249.2012.730321]

5 Chapel A, Bertho JM, Bensidhoum M, Fouillard L, Young RG, Frick J, Demarquay C, Cuveller F, Mathieu E, Trompier F, Dudoignon N, Germain C, Mazurier C, Aigueperse J, Borneman J, Gorin NC, Gourmelon P, Thierry D. Mesenchymal stem cells homed to injured tissues when engineered with hematopoietic cells to treat a radiation-induced multi-organ failure syndrome. J Gene Med 2003; 5: 1028-1038 [PMID: 14661178]

6 Bensidhoum M, Chapel A, Francois S, Demarquay C, Mazurier C, Fouillard L, Bouchet S, Bertho JM, Gourmelon P, Aigueperse J, Charbord P, Gorin NC, Thierry D, Lopez M. Homing of in vitro expanded Stro-1 or Stro-1+ human mesenchymal stem cells into the NOD/SCID mouse and their role in supporting human CD34 cell engraftment. Blood 2004; 103: 3313-3319 [PMID: 14715641 DOI: 10.1182/blood-2003-04-1121]

7 François S, Bensidhoum M, Mouiseddine M, Mazurier C, Allenet B, Semont A, Frick J, Saché A, Bouchet S, Thierry D, Gourmelon P, Gorin NC, Chapel A. Local irradiation not only induces homing of human mesenchymal stem cells at exposed sites but promotes their widespread engraftment to multiple organs: a study of their quantitative distribution after irradiation damage. Stem Cells 2006; 24: 1020-1029 [PMID: 16339642 DOI: 10.1634/stemcells.2005-0260]

8 Mouiseddine M, François S, Semont A, Saché A, Allenet B, Mathieu N, Frick J, Thierry D, Chapel A. Human mesenchymal stem cells home specifically to radiation-injured tissues in a non-obese diabetic/severely combined immunodeficiency mouse model. Br J Radiol 2007; 80 Suppl No 1: 549-555 [PMID: 17704326 DOI: 10.1259/bjr/25970574]

9 François S, Mouiseddine M, Mathieu N, Semont A, Monti P, Dudoignon N, Saché A, Bourtarfa A, Thierry D, Gourmelon P, Chapel A. Human mesenchymal stem cells favour healing of the cutaneous radiation syndrome in a xenogenic transplant model. Ann Hematol 2007; 86: 1-8 [PMID: 17043780 DOI: 10.1007/s00277-006-0166-5]

10 Bensidhoum M, Gobin S, Chapel A, Lemaître G, Bouet S, Waksman G, Thierry D, Martin MT. Therapeutic effect of human bone marrow and venous human mesenchymal stem cells engraftment following autologous haematopoietic stem cell transplantation. Leukemia 2007; 21: 568-570 [PMID: 17252011 DOI: 10.1038/sj.leu.2404550]

11 Nafse A, Chapel A, Mazurier C, Bouchet S, Lopez M, Mathieu N, Sersée L, Zhang Y, Gorin NC, Thierry D, Fouillard L. Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells. Gene Exp 2007; 13: 217-226 [PMID: 17605296 DOI: 10.7177/0100000678666957]

12 Nafse A, Mathieu N, Chapel A, Frick J, François S, Mazurier C, Bourtarfa A, Bouchet S, Gorin NC, Thierry D, Fouillard L. Immunosuppressive effects of mesenchymal stem cells: involvement of HLA-G. Transplantation 2007; 84: 231-237 [PMID: 17667815 DOI: 10.1097/tp.0b01200526978b08]

13 Nafse A, Mazurier C, Bouchet S, François S, Chapel A, Thierry D, Gorin NC, Fouillard L. Leukemia inhibitory factor: Role in human mesenchymal stem cells mediated immunosuppression. Cell Immunol 2008; 253: 16-22 [PMID: 18639869 DOI: 10.1016/j.cellimm.2008.06.002]

14 Nafse A, Zhang YZ, Mazurier C, Bouchet S, Bensidhoum M, François S, Gorin NC, Lopez M, Thierry D, Fouillard L, Chapel A. Selected Stro-1 enriched bone marrow stromal cells display a major suppressive effect on lymphocyte proliferation. Int J Lab Hematol 2009; 31: 9-19 [PMID: 19143868 DOI: 10.1111/j.1751-553X.2007.00997.x]

15 Kobari L, Yates F, oudhiri N, Francina A, Kiger L, Mazurier C, Rouzbeh S, El-Nemer W, Hebert N, Giarratana MC, François S, Chapel A, Lapillonne H, Luton D, Bennaceur-Griscelli A, Douay L. Human induced pluripotent stem cells display a major suppressive effect on lymphocyte proliferation. Int J Lab Hematol 2009; 31: 9-19 [PMID: 19143868 DOI: 10.1111/j.1751-553X.2007.00997.x]

16 Larbi A, Gombert JM, Auvray C, l’Homme B, Magniez A, Féraud O, Coulombel L, Chapel A, Mittjavila-Garcia MT, Turhan AG, Haddad R, Bennaceur-Griscelli A. The JOXH4i homeoprotein promotes the ex vivo enrichment of functional human embryonic stem cell-derived NK cells. PLoS One 2012; 7: e93514 [PMID: 22761810 DOI: 10.1371/journal.pone.0093514]

17 Che TC, François S, Bouchet S, Chapel A, Forgue-Lafitte ME. Early lesions induced in rat colon epithelium by N-methyl-N’-nitro-N-nitrosoguanidine. Tissue Cell 2010; 42: 190-194 [PMID: 20495388]

18 Lalaitable JD, Doucet C, Bey E, Carsin H, Huet C, Clairand I, Bottollier-Depoix JP, Chapel A, Emrou I, Gourven M, Boutin L, Hayden A, Carcano C, Buglova E, Joussemet M, de Revel T, Gourmelon P. New approach to radiation burn treatment by dosimetry-guided surgery combined with autologous mesenchymal stem cell therapy. Regen Med 2007; 2: 785-794 [PMID: 17907931 DOI: 10.2217/17460751.2.5.785]

19 Voswinkel J, François S, Simon JM, Benderitter M, Gorin NC, Mothly M, Fouillard L, Chapel A. Use of Mesenchymal Stem Cells (MSC) in Chronic Inflammatory Fistulizing and
Fibrotic Diseases: a Comprehensive Review. *Clin Rev Allergy Immunol* 2013 Jan 8; Epub ahead of print [PMID: 23296948 DOI: 10.1007/s12016-012-8347-6]

Fouillard L, Bensidhoum M, Bories D, Bonte H, Lopez M, Moseley AM, Smith A, Lesage S, Beaujean F, Thierry D, Gourmelon P, Najman A, Gorin NC. Engraftment of allogeneic mesenchymal stem cells in the bone marrow of a patient with severe idiopathic aplastic anemia improves stroma. *Leukemia* 2003; 17: 474-476 [PMID: 12592355 DOI: 10.1038/sj.leu.2402786]

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