Autologous bone marrow stromal cell transplantation as a treatment for acute radiation enteritis induced by a moderate dose of radiation in dogs

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Radiation enteritis is one of the most common complications of cancer radiotherapy, and the development of new and effective measures for its prevention and treatment is of great importance. Adult bone marrow stromal stem cells (ABMSCs) are capable of self-renewal and exhibit low immunogenicity. In this study, we investigated ABMSC transplantation as a treatment for acute radiation enteritis. We developed a dog model of acute radiation enteritis using abdominal intensity-modulated radiation therapy in a single X-ray dose of 14 Gy. ABMSCs were cultured in vitro, identified via immunofluorescence and flow cytometry, and double labeled with CM-DiI and superparamagnetic iron oxide (SPIO) before transplantation, which took place 48 hours after abdominal irradiation in a single fraction. The dog model of acute radiation enteritis was transplanted with cultured ABMSCs labeled with CM-DiI and SPIO into the mesenteric artery through the femoral artery. Compared with untreated control groups, dogs treated with ABMSCs exhibited substantially longer survival time and improved relief of clinical symptoms. ABMSC transplantation induced the regeneration of the intestinal epithelium and the recovery of intestinal function. Furthermore, ABMSC transplantation resulted in elevated serum levels of the anti-inflammatory cytokine interleukin-11 (IL10) and intestinal radioprotective factors, such as keratinocyte growth factor, basic fibroblast growth factor-2, and platelet-derived growth factor-B while reducing the serum level of the inflammatory cytokine IL17. ABMSCs induced the regeneration of the intestinal epithelium and regulated the secretion of serum cytokines and the expression of radioprotective proteins and thus could be beneficial in the development of novel and effective mitigators of and protectors against acute radiation enteritis. (Translational Research 2016;171:38–51)

Abbreviations: ABMSCs = adult bone marrow stromal stem cells; IMRT = intensity-modulated radiation therapy; SPIO = superparamagnetic iron oxide; IL10 = interleukin-11; KGF = keratinocyte growth factor; FGF-2 = basic fibroblast growth factor-2; PDGF-B = platelet-derived growth factor-B; IL17 = interleukin-17; GI = gastrointestinal; BMSCs = bone marrow stromal stem cells; MSCs = mesenchymal stem cells; PTV = planning target volume; DVH = dose-volume histogram; CT = computed tomography; DAO = O-dianisidine; PE = phycoerythrin; DMSO = dimethyl sulfoxide; FBS = fetal bovine serum; FITC = fluorescein isothiocyanate; MTT = 3-(4,5)-dimethylthiazol-z-yl)-

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2,5-diphenyltetrazolium bromide; FCM = flow cytometry; DAPI = 4′,6-diamidino-2′-phenylindole dihydrochloride; BSA = bovine serum albumin; PBS = phosphate-buffered saline; ELISA = enzyme-linked immunosorbent assay; TEM = transmission electron microscopy; HE = hematoxylin and eosin; ECL = enhanced chemiluminescence; HRP = horseradish peroxidase; FACS = fluorescence-activated cell sorting; DSA = digital subtraction angiography; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IGF-I = insulin-like growth factor; SDF-I = stromal cell-derived factor-1; CM-DiI = chlormethylbenzamido-1,1dioctadecyl-3,3,3′,3′-tetramethylindocarbocyamine; BCA = bicinchoninic acid; SDS-PAGE = sodium dodecyl sulfate-polyacrylamide gel electrophoresis; PVDF = polyvinylidene fluoride; ANOVA = analysis of variance; FDA = food and drug administration; XWD = Xu Wen-DA; SDS-PAGE = sodium dodecyl sulfate-polyacrylamide gel electrophoresis

AT A GLANCE COMMENTARY

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Background

Radiation enteritis is the very common side effect of radiation of abdominal or pelvic malignancies. At least 75% of patients undergoing abdominal or pelvic radiation therapy will suffer from side effects. Although radiation enteritis is the hot topic for decades, valid reports on treatment are lacking.

Translational Significance

In this article, we show that adult bone marrow stromal stem cells transplantation could mitigate clinical manifestations of acute radiation enteritis induced by a moderate abdominal radiation dose. Adult bone marrow stromal stem cells transplantation can result in structural and functional recovery of damaged intestine and changes of the serum cytokines and protein growth factors.

INTRODUCTION

Accidental or intended radiation exposure in a mass-casualty setting presents a serious and ongoing threat. The gastrointestinal (GI) tract is the second-most sensitive organ, after bone marrow, to damage from moderate-dose radiation exposure. Radiation enteritis is a common side effect of radiation used to treat abdominal or pelvic malignancies. At least 75% of patients undergoing abdominal or pelvic radiation therapy will suffer from side effects. Moreover, the degree of radiation enteritis and the rate of survival depend on exposure dose and duration. The consequences of radiation enteritis may result in considerable morbidity, including acute and chronic symptoms. Although radiation-induced injury to the GI tract has attracted considerable attention over decades, valid data on the treatment of radiation enteritis are lacking. Treatment is primarily symptomatic; however, the potential severity of the disorder creates a need for novel, effective therapeutic strategies. Cell therapy may be an alternative for the treatment of early and late radiation-induced normal tissue injury.[1]

Earlier reports demonstrated that donor bone marrow–derived cells could contribute to multiple lineages in the GI tract and facilitate intestinal regeneration in patients with graft-vs-host disease and ulcers[2]; similar responses have been observed in animal models of colitis and GI syndrome.[3] Because they are easy to grow in cell culture and can differentiate into multiple tissue lineages, the transplantation of bone marrow stromal stem cells (BMSCs) is an attractive option for a wide range of clinical applications[4]; however, until now, transplantation of whole bone marrow or mesenchymal stem cells (MSCs) has been successful in ameliorating radiation enteritis and improving the survival in rodent and large animal models that received high doses of irradiation in a single fraction.[5-11] We reasoned that the failure of cell-based therapies in ameliorating radiation enteritis after lethal doses of irradiation may be attributable to the multisystem damage caused by irradiation. Therefore, large animal models of radio-induced enteritis and MSC therapy are needed to ensure the validity of experimental results, as described by Linard et al.[11] In a previous study, we developed a dog model of acute radiation enteritis caused by various doses of abdominal irradiation administered by intensity-modulated radiation therapy (IMRT), thereby avoiding damage to other organ systems.[12] In the present report, we demonstrate that adult BMSC (ABMSC) transplantation 48 hours after exposure to a moderate radiation dose of 14 Gy relieved clinical symptoms, prolonged survival time, improved bowel function, restored the functional integrity of the villi, and dampened the inflammatory response in dogs.

MATERIALS AND METHODS

Animals and ethics statement. Female beagles aged 11–26 months weighing 12.03 ± 0.53 kg were used in the experiment after 1 week of adaptive feeding in the laboratory. The animals were obtained from the