Characterization of a Minipig Model of Gastrointestinal Acute Radiation Syndrome Using Total Body Irradiation and Partial Body Irradiation: A Focus on Intestinal Pathology

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Introduction

Accidental or intentional acute exposure of humans to irradiation is increasingly of concern due to the inherent risk of developing acute radiation injury primarily manifested as gastrointestinal and/or hematopoietic acute radiation syndrome (ARS). There is ongoing research in an attempt to find potential remedies that can mitigate gastrointestinal acute radiation syndrome (ARS) outcome. Most research to date has focused on the use non human primates and mice. However, the gastrointestinal (GI) tract of minipigs presents similarities with humans including intestinal transit time, adaptation to an omnivore diet and humidity content of feces which impacts the bacterial flora. This report documents characteristic gastrointestinal ARS-related GIT lesions in minipigs following PBI and TBI. Thus, the minipig model could be used to evaluate potential therapies for GIT-ARS.

Materials and Methods

One male Gottingen minipig was assigned to each of three groups. Group 1 served as a non-irradiated control. Group 2 (PBI) and 3 (TBI) were exposed to gamma radiation from a Co60 source (Theratron1000). animals were irradiated with a single dose up to 12Gy, delivered in 2 lateral fractions at a dose rate of 50cGy/min.

Dosimetry measurements were made in experimental conditions using a custom-made mini-pig acrylic phantom, a solid water phantom with Markus and Farmer ionization chambers. Each animal was irradiated with a single dose up to 12 Gy, delivered in 2 lateral fractions, one on each side. In the PBI set-up, Cerrobend shielding (9 cm) provided attenuation of the dose delivered to the minipig pelvic legs with the resulting bone marrow dose under 7 % of the midplane dose delivered to the body. Nanodots and superflab buildup material were used to validate the treatment dose and protected bone marrow dose. A minipig acrylic phantom was used to produce adequate dose scattering conditions. Real-time, in-vivo dosimetry was implemented during animal exposure using a Farmer chamber subjected to an electrometer bias voltage of -300V confirming accuracy under 2% of prescribed dose. Pigs were euthanized and necropsied following 7 days of observation. The small intestines, colon, rectum sternum and abnormal findings were routinely processed to slides, stained with H&E and evaluated microscopically.

Results

Emesis up to several days after radiation and partial to complete anorexia were consistently observed. Bone marrow shielding resulted in a significant attenuation of radiation induced bone marrow depletion with higher counts after PBI compared to TBI for all lineages. In decreasing order, the most important protective effects were noted in lymphocytes, neutrophils, reticulocytes and platelets.

At necropsy, dark red areas/foci consistent with hemorrhages were observed in the gastrointestinal tract. Microscopic evaluation confirmed minimal to moderate loss/atrophy of intestinal crypts in most GI segments with villous atrophy in the small intestines of up to 70-80% compared to sham irradiated minipigs. Intestinal crypt degeneration/regeneration was observed in the small and large intestines. In addition, erosions and ulcerations considered as hallmarks of GI-ARS were noted in all GI segments (i.e. stomach, small and large intestines) at Day 7 post-exposure. The overall mononuclear cellularity (lymphocyte, plasma cell etc.) in the gastrointestinal lamina propria was decreased with both TBI and PBI. Evidence of bacterial colonization were noted in the intestines and stomach, with bacteria often seen attaching to and effacing the intestinal brush border in both TBI and PBI. Hemorrhages were noted in several tissues but were more widespread after TBI suggesting protective effects of bone marrow sparing with PBI on this sequelae. Other classical irradiation-related changes observed in this model included lymphoid atrophy in lymph nodes and thymus, as well as hematopoietic hypocellularity in the bone marrow in PBI and/or TBI pigs.

Conclusion

In conclusion, while the monkey and mouse are currently the most common species used to assess gastrointestinal acute radiation syndrome therapies, it is believed that the minipig can be a valuable alternative due to it close similarities to human in gastrointestinal transit time, adaptation to an omnivore diet and humidity content of feces which impacts the bacterial flora. The minipig is therefore a potentially valuable model for GI-ARS treatments. An irradiation set-up was designed for total body irradiation (TBI) and partial body irradiation (PBI) in conscious minipigs.