FGF-PT as a Mitigator of Acute Radiation Syndromes in Multi-Organ Systems

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Basic fibroblast growth factor (FGF2) has been shown to enhance the preservation and proliferation of progenitor cells and maintenance of normal cellular maturation and function in multiple organ systems after irradiation (IR). Receptors for FGF2 are present on hematopoietic, gastrointestinal, and cutaneous progenitor cells. Therefore, we assessed the ability of a 17 amino acid FGF2 mimetic, FGF-PT, to reduce the lethality of bone marrow and gastrointestinal acute radiation syndromes (H-ARS and GI-ARS, respectively) and for cutaneous radiation injury (CRI) in combination with H-ARS. Studies were done in both mouse and rat models.

The efficacy of FGF-PT as a mitigator was assessed in total body irradiation (TBI) H-ARS, sub-TBI (5% bone marrow sparing GI-ARS), and CRI (TBI + double 75 Gy beta radiation skin wound) models. Both NIH Swiss mice and Wistar Han IGS rats were used in various studies. The efficacy of FGF-PT in enhancing survival was evaluated in animals irradiated to doses representing lethal dose (LD)20/30 to LD70/30 (H-ARS), LD50/10 to LD90/10 (GI-ARS), or LD20/30 to LD70/30 TBI (CRI) and receiving FGF-PT in subcutaneous (SC) doses of 2.5 to 10 mg/kg (3 daily doses) beginning 24 hr after IR. Survival, weight changes, diarrhea, blood counts, and inflammation and cellular function biomarkers were evaluated 30 days postirradiation. To evaluate expected concomitant therapy, FGF-PT was also examined with and without Neupogen at 100 ug/kg SC on day 1 and day 8.

All SC doses (2.5–10 mg/kg) of FGF-PT provided substantial survival benefits in H-ARS and GI-ARS in mice and rats. The optimal dose appears to be between 5 and 10 mg/kg. Time to nadir in weight, the rate of weight loss, weight recovery time, and the onset and duration of diarrhea were not found to be predictors of survival. White blood cell counts generally showed improved recovery in FGF-PT treated animals with or without Neupogen. Human recombinant FGF2 was used as a positive control in some studies. FGF-PT provided improvements in cellular function (e.g., increased mitochondrial content and function, increased telomere length) compared to controls. Animals in the CRI model showed improved survival benefits with FGF-PT and accelerated healing of radiation-induced skin wounds. Circulating inflammatory cytokine levels were generally decreased in FGF-PT treated animals compared to controls. By contrast, rats treated with Neupogen but not FGF-PT did not have an improved immune state 30 days after IR. Similar benefits are seen in both males and females.

FGF-PT delivered 24 hr after IR produced survival benefits in H-ARS, GI-ARS, and CRI models.