Enhanced survival of lethally irradiated mice given pegylated G-CSF, GM-CSF, and IL-11 with lisinopril via modulation of the hematopoietic cytokines TGFβ-1 and RANTES

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Background and Hypothesis:

We have previously shown increased survival in mice given pegylated growth factors, G-CSF, GM-CSF, and IL-11 (triple combo, TC), with lisinopril compared to TC alone in the hematopoietic acute radiation syndrome (H-ARS). This experiment investigated the mechanism behind the survival benefit. We hypothesized lisinopril regulates inflammatory cytokines hence increasing quiescence of primitive bone marrow cells.

Experimental Design or Project Methods:

C57BL/6 mice were exposed to LD90/30 total body irradiation (TBI). The irradiated mice were given a TC injection on day 1, and lisinopril was administered in drinking water beginning on day 7. Mice were euthanized on day 10. Flow cytometry was used to analyze bone marrow cell cycle and Bioplex was used to analyze cytokines in bone marrow supernatant.

Results:

Treatment with TC+lisinopril significantly decreased the level of the pro-inflammatory cytokine RANTES compared with vehicle mice (Veh) and TC alone (TC+Liso vs. Veh: 3.6 vs. 7.8 pg/mL, $p<0.01$; TC+Liso vs. TC: 3.6 vs. 5.2 pg/ml, $p<0.01$). TC+lisinopril increases levels of the pro-quiescence cytokine TGF-β1, compared with Veh and TC alone (TC+Liso vs. Veh: 92.8 vs. 45.6 pg/mL, $p<0.05$; TC+Liso vs. TC: 92.8 vs. 44.7 pg/ml, $p<0.01$). TC alone had lower percentages of quiescent Lin- primitive bone marrow cells (G0+G1) than non-irradiated (NI) mice (75.7 vs. 85.2%, $p<0.05$), whereas there is no difference between TC+Liso and NI mice (83.0 vs. 85.2%, $p=0.44$).

Conclusion and Potential Impact:

The increased survival of H-ARS mice given lisinopril might be due to the regulation of TGF-β1 and RANTES levels in the bone marrow leading to quiescence of primitive bone marrow cells.