

Cytokines to treat casualties involved in nuclear & radiological events: gold standard and new perspectives

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Counteracting the hematopoietic syndrome following accidental or intentional irradiation remains an important therapeutic challenge. However, the pathophysiology of accidental irradiation has been recently revisited. Indeed irradiation has to be considered as a global illness that is more complex than the juxtaposition of single syndromes. This was especially illustrated in the Tokai-Mura case where the two highly irradiated victims died from a complex multiorgan distress then failure syndrome (MODS/MOFS) in spite of transient hematopoietic chimerism following hematopoietic stem cell transplantation. Radiation burns were especially involved in this MOF development. In fact, the pathophysiology of MODS strongly overlaps the systemic inflammatory response syndrome that is mainly the consequence of extensive endothelial cell damage. Clearly, there is a need to develop new therapeutic strategies to counter such radiation-induced extrahematological toxicity, in addition to correcting hematopoietic disorders. Regarding hematopoiesis, the rationale of cytokine/hematopoietic growth factor use is the heterogeneity of bone marrow damage in most documented accidents. Today, early administration of granulopoietic factors is recommended to stimulate residual hematopoiesis in victims irradiated at intermediate dose levels. In complement our group proposes the emergency antiapoptotic cytokine (EACK) therapy in case of high dose irradiation, which consists in preserving and stimulating residual hematopoietic stem and progenitor cells following irradiation. We selected the stem cell factor + Flt-3 ligand + thrombopoietin + interleukin-3 + PegG-CSF antiapoptotic combination that is capable of abrogating thrombocytopenia and reducing neutropenia when given as an early single administration in highly irradiated monkeys (7 Gy gamma) 2 hrs after total body irradiation. Regarding extrahematological toxicity, injection of Keratinocyte growth factor or erythropoietin could be a flexible cytokine complementary/alternative approach to cell therapy (i.e. mesenchymal stem cells grafting). We recently re-evaluated the benefit of using erythropoietin (Epo) as a pleiotropic cytokine to counteract hematologic and extra-hematologic toxicity following lethal irradiation. B6D2F1 mice were globally exposed to 9 Gy gamma (LD90%/30days) and then injected with SFT3 at 2 hours + 24 hours with or without Epo (1000-3000 UI/kg) at 2 hours + 8 days. Epo synergized with SFT3 to rescue lethally irradiated mice from radiation-induced death (60%, 95% and 5% respectively for SFT3, SFT3+Epo and controls at 30 days) whereas Epo alone exhibited no protective effect. Interestingly, hematopoietic parameters did not significantly differ between SFT3 and SFT3+Epo groups. This suggests predominant extra-hematological targets for Epo. Ongoing studies aim at improving EACK strategy in terms of tolerance and efficacy.