The lethality of radiation-induced sepsis and associated immune dysregulation highlight the importance of restoring lymphocyte and monocyte levels and function after total body irradiation (TBI)

John McManus

Partner Therapeutics, Inc., Lexington, MA, USA

Abstract

Human experience and animal data generated in well-controlled models indicate that sepsis and associated immune dysregulation are primary contributors to mortality after TBI. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection or injury characterized by altered immune homeostasis and disruption of resistance, tolerance, resilience, and resolution mechanisms. Data from radiation victims experiencing Acute Radiation Syndrome (ARS) indicate impaired function of lymphocytes in the bone marrow (BM) and circulation. This has been attributed to persistent BM and lymphatic system damage and defects in antigen presentation by macrophages and lymphopenia.

In two GLP studies in an NHP-model of TBI ($LD_{50\text{-}60/60}$-$LD_{70\text{-}80/60}$), sepsis was identified as the primary probable cause of death in 111 of 115 control decedents (97%). Control decedents presented with severe BM hypocellularity and atrophy of the spleen, thymus and lymph nodes. Absolute lymphocyte count (ALC) became severe (<0.50 $x10^9$/L) by Day 2 and absolute monocyte count (AMC) became severe (<0.10 $x10^9$/L) by Day 4. ALC and AMC remained suppressed until death for 97% and 94% of decedents.

In the primary study that supported FDA approval for H-ARS, treatment with sargramostim (rhu GM-CSF) reduced the incidence of sepsis from 63% to 17% and reduced the frequency and severity of BM hypocellularity and lymphatic system atrophy as well as the duration of severe lymphopenia. ALC nadir with treatment occurred earlier and at a higher level.

Pilot studies in sepsis patients suggest that sargramostim restores immune response and function measured by monocyte HLA-DR expression, TNFα production capacity and neutrophil function. This was accompanied by benefit in clinical outcomes as measured by 28-day survival, hospital discharge and reduced infection.

In conclusion, sepsis, BM and lymphatic damage, and immune suppression were strongly associated with mortality, and sargramostim treatment significantly improved survival (p=0.0018; p=0.0032), reduced the frequency of sepsis, and accelerated recovery of immune function as measured by ALC and AMC. This highlights the commensurate importance of restoring lymphocyte and monocyte count and function to reduce frequency and severity of sepsis and improve outcomes in ARS.