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)

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Abstract

Human experience and data from well-controlled animal models indicate sepsis and associated immune dysregulation are primary contributors to mortality after total body irradiation (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. Victims of Acute Radiation Syndrome (ARS) experience impaired function of lymphocytes in the bone marrow (BM) and circulation. This has been attributed to reduced frequency and impaired function of circulating mononuclear cells, resulting in persistent damage to the lymphatic system and defective antigen presentation by monocytes/dendritic cells.

Acute Radiation Syndrome (ARS)

ARS occurs when individuals are exposed to high doses of TBI that causes multiorgan injury. Exposure to high-dose whole-body ionizing radiation induces dose-dependent damage to the BM, spleen, thymus, lymph nodes and blood cells, resulting in pancytopenia. Low white blood cell counts, including lymphocytes, eosinophils, monocytes, and neutrophils, culminate in immunosuppression that leads to bacterial, viral, and fungal infections and ultimately sepsis. Significant causes of death among patients with ARS include infection, sepsis, uncontrollable bleeding, and severe acute anemia, all of which contribute to multi-organ dysfunction and failure (MOD/MOF) (Wolbarst 2010, Dainiak 2018).

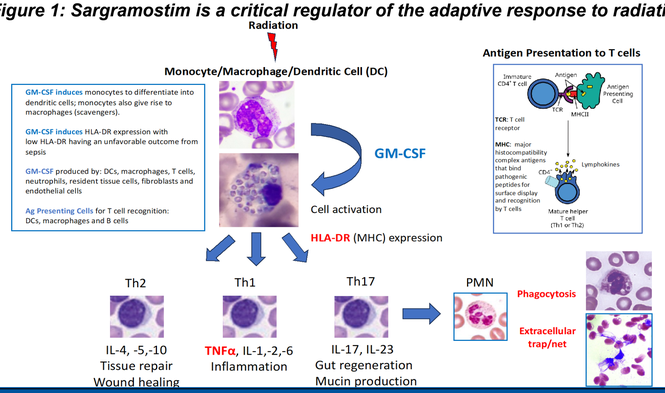
Sepsis

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection characterized by altered immune homeostasis. It represents a critical unmet health need urgently requiring safe and effective therapeutics guided by biomarkers to enable precise treatment approaches to reduce morbidity and mortality.

Sargramostim (Leukine® / rhu GM-CSF)

Sargramostim stimulates proliferation, differentiation, and maturation of cells involved in innate and adaptive immune response, including, but not limited to, granulocytes, monocytes, macrophages, megakaryocytes, and dendritic cells (Leukine USPI). Sargramostim drives host immunity by boosting innate and adaptive host defense and targets epithelial repair and restoration, including in the lungs and GI tract (Rosler 2016, Bernasconi 2010).

Figure 1: Sargramostim is a critical regulator of the adaptive response to radiation



Radiation-Induced Sepsis in NHP TBI H-ARS Model

In two GLP studies (TSK-0144, 1017-3493) in an NHP-model of TBI (LD50-60/60-LD70-80/60), sepsis was identified as a primary probable cause of death in 111 of 115 control decedents (97%) (Figure 2). Control decedents presented with marked to severe BM hypocellularity and severe atrophy of the spleen, thymus and lymph nodes (Figure 3).

Figure 2: Probable Cause of Death

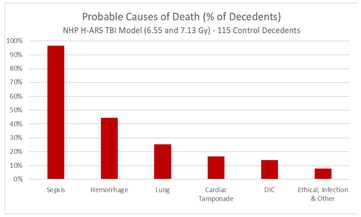
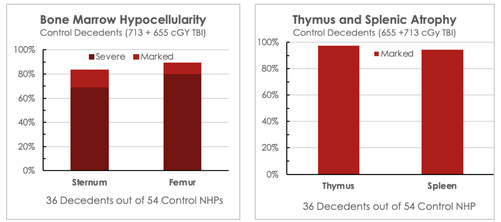


Figure 3: BM Hypocellularity/Thymus & Splenic Atrophy



Sargramostim Effect on Radiation-Induced Sepsis

In the primary study (TSK-0144) that supported FDA approval for H-ARS, treatment with sargramostim 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. Absolute lymphocyte Count (ALC) nadir with treatment occurred earlier and at a higher level. 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 (TSK-0144, 1017-3493).

Figure 4: Reduced Mortality/Sepsis

Probable Cause of Death for Unscheduled Euthanasia or Subjects Found Dead

	Total - Percent of All Animals					
	6.55 Gy		7.13 Gy		Combined	
	Control	Leukine	Control	Leukine	Control	Leukine
Total Animals per Group	36	36	18	18	54	54
Day 60 Mortality	58%	22%	83%	39%	67%	28%
Sepsis	53%	14%	83%	22%	63%	17%
Hemorrhage	31%	17%	50%	22%	37%	19%
Cardiac Tamponade	8%	3%	33%	0%	17%	2%
DIC	8%	3%	6%	6%	7%	4%
Pneumonia/Lung Edema	6%	3%	11%	11%	7%	6%
Infection	11%	0%	0%	0%	7%	0%
Anemia	3%	8%	6%	6%	4%	7%
Ethical/Non-Radiation	0%	6%	0%	11%	0%	7%

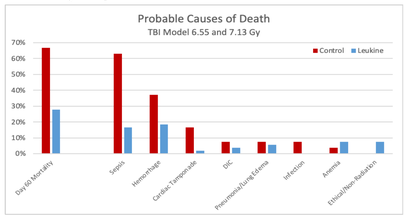


Figure 5: Reduced BM Hypocellularity

Bone Marrow Hypocellularity: Femur & Sternum (Decedents) 655 cGy

	Leukine Males	Control Males	Leukine Females	Control Females
Severe	1	7	5	11
Marked	0	1	0	0

Bone Marrow Hypocellularity: Femur & Sternum (Decedents) 713 cGy

	Leukine Males	Control Males	Leukine Females	Control Females
Severe	2	5	2	7
Marked	0	1	1	1

Figure 6: Reduced Thymic/Splenic Atrophy

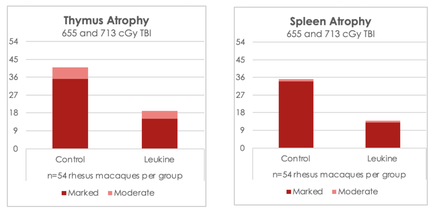


Figure 7: Enhanced Lymphocyte Recovery

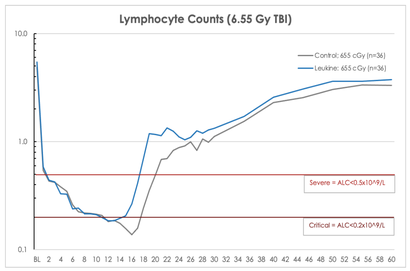
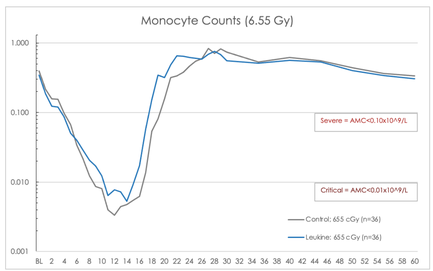


Figure 8: Enhanced Monocyte Recovery



Sargramostim Potential in Radiation/Sepsis Immunosuppression

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 improvement was accompanied by benefit in clinical outcomes as measured by 28-day survival, hospital discharge and reduced infection (Figure 9).

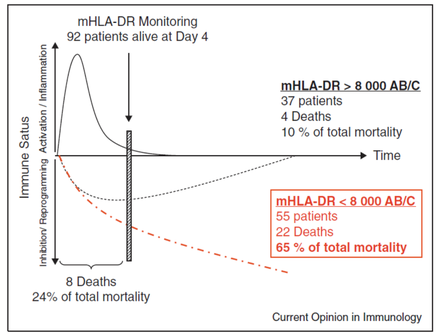
Figure 9: Clinical Studies of Sargramostim in Severe Sepsis, Septic Shock and Critical Care

	Patient Population	mHLA-DR Measured	mHLA-DR for Patient Selection	Sub-group Analysis	GM-CSF ↑ mHLA-DR	Clinical Response
Vacheron 2023	Severe sepsis or septic shock	Yes	Yes[1]	Yes	Yes	Trend
Hassan 2023	Neonatal sepsis	No	No[2]	NA	NA	Trend
Pinder 2018	ICU w/ SIRS and Organ Support	Yes	No[3]	No	Yes	Trend
Spies 2015	Post-surgery	Yes	Yes[4]	Yes	Yes	Yes
Hall 2011	Pediatric sepsis w/ MODS	Yes	No	Yes	Yes[5]	Yes
Meisel 2009	Severe sepsis or septic shock	Yes	Yes[6]	Yes	Yes	Yes
Rosenbloom 2005	ICU w/ SIRS but not shock	Yes[7]	No	Yes	Yes	Trend

1) mHLA-DR<8,000 antibodies bound per cell on day 3 after ICU admission was used for patient selection; 2) ANC<1,500 cells/mm was used for patient selection/subgroup analysis; 3) Neutrophil phagocytic capacity <50% was used for patient selection; 4) mHLA-DR<10,000 antibodies per cell on the day after esophageal or pancreatic resection surgery was used for patient selection; 5) Sargramostim increased ex-vivo TNFα response and mHLA-DR response was correlated with TNFα response; 6) mHLA-DR<8,000 antibodies per cell (AB/C) in two consecutive measurements (2 days before enrollment) was used for patient selection; 7) Percent of HLA-DR positive monocytes beginning on Day 0 (diagnosis with sepsis).

Monneret & Venet evaluated 100 septic shock patients in a virtual clinical study and reviewed mHLA-DR levels at Day 1-2, 3-5 and 7-10. Patients were stratified based on a previously established threshold for mHLA-DR on Day 3-5 (< or ≥ 8,000 AB/C). Eight patients died during the first 3 days. Of the 92 patients alive at Day 3-5, 60% (55) had mHLA-DR below the threshold. Sargramostim has been studied in small randomized clinical trials in sepsis, septic shock and critical care, where it has proved to be safe and associated with rapid and sustained improvement in monocyte HLA-DR (Venet 2013) (Figure 9).

Figure 10: Septic shock patients stratified by mHLA-DR: a vitrual cohort based on real data (Venet 2013)



Sargramostim has also enhanced immune response in septic patients with dysregulated or suppressed immune response as indicated by markers such as HLA-DR and/or TNF-a production capacity (Rosenbloom 2005, Nelson 2007, Meisel 2009, Schefold 2010, Hall 2011, Leentjens 2012, Pinder 2018). GM-CSF has known effects on stimulating both neutrophil and monocyte production and function (Dougan 2019, Clayton 2021), as well as promoting balance in T regulatory and T effector cells in Parkinson's disease (Gendelman 2017, Olson 2021).

Conclusions

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 (TSK-0144, 1017-3493). 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.

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COI: JM is employed by and has stock options for Partner Therapeutics, Inc. ILJ and ND are paid consultants for Partner Therapeutics.

References available, contact: John.McManus@partnertx.com